Notice/Disclaimer: The clinical information contained herein is provided for the express purpose of aiding the Pharmacy and Therapeutics ("P&T") Committee members in reviewing medications for inclusion in or exclusion from the Virginia Preferred Drug List. This information is not intended nor should it be used as a substitute for the expertise, skill, and judgment of physicians, pharmacists, or other healthcare professionals. The absence of a warning for any given drug or drug combination should not be construed to indicate that the drug or drug combination is safe, appropriate or effective for any given patient. This information is intended to supplement the knowledge and additional resources available to the P&T Committee members and should not be considered the sole criteria used by the P&T Committee in deciding what medications will be included or excluded from the Virginia Preferred Drug List.

TABLE OF CONTENTS

Drug Class Reviews

Inhaled Corticosteroids					
Characteristic	**Qvar (beclomethasone)**	**Pulmicort Turbuhaler, Pulmicort Respules (budesonide)**	**AeroBid, AeroBid-M (flunisolide)**	**Flovent, Flovent Rotadisk (fluticasone)**	**Azmacort (triamcinolone)**
Pharmacology	Inhaled corticosteroids have anti-inflammatory effects of the bronchial mucosa of asthma patients. Treatment with inhaled corticosteroids for 1 to 3 months results in a reduction in mast cells, macrophages, T-lymphocytes, and eosinophils in the epithelium and submucosa in the bronchioles. By reducing airway inflammation, inhaled corticosteroids lessen airway hyperresponsiveness in asthmatic adults and children. Long-term therapy reduces airway responsiveness in asthmatic histamine cholinergic agonists, and allergens. Treatment also lowers responsiveness to exercise, fog, cold air, bradykinin, adenosine, and irritants. Inhaled corticosteroids make the airways less sensitive to these spasmogens and limits the maximal narrowing of the airway. Maximal effects of inhaled corticosteroid treatment may not be seen for several weeks.				
Generic formulation available?	No	No	No	No	No
Date of FDA Approval	9/15/00	6/29/97-Turbohaler 8/8/00-Respules	8/17/84	3/27/96	4/23/82
Manufacturer	Ivax	Astrazeneca	Forest	GlaxoSmithKline	Aventis
Dosage forms available	**HFA:** 40 mcg/actuation in 7.3 g canisters. 80 mcg/actuation in 7.3 g canisters **Note:** Due to the smaller particle size of QVAR (an HFA product) the dose equivalent is ½ that of the former CFC beclomethasone products	**Turbuhaler:** Powder:200 mcg (each actuation delivers 160mcg)/metered dose **Respules: Inhalation suspension for nebulization:** 0.25mg/2mL in single dose envelopes of 30 0.5mg/2mL in single dose envelopes of 30	**AeroBid Aerosol:** 250mcg/actuation **AeroBid-M**: Menthol flavor: 250mcg/actuation	**Flovent: Aerosol** 44mcg/actuation, 110mcg/actuation, 220mcg/actuation **Flovent Rotadisk Powder** 50mcg/actuation, 100mcg/actuation, 250mcg/actuation **Flovent Diskus Powder for inhalation:** FDA approved, but not marketed	**Azmacort Aerosol** 100mcg/actuation from spacer mouthpiece

Inhaled Corticosteroids					
Characteristic	**Qvar (beclomethasone)**	**Pulmicort Turbuhaler, Pulmicort Respules (budesonide)**	**AeroBid, AeroBid-M (flunisolide)**	**Flovent, Flovent Rotadisk (fluticasone)**	**Azmacort (triamcinolone)**
Number of Actuations (puffs or inhalations) per cannister/Size of canister	**HFA:** Both strengths have 100 actuations per 7.3g canister	**Turbuhaler**: In 200 doses per turbohaler. **Inhalation Suspension:** EDTA. In single-dose envelopes. In 30s	**Aerosol:** 100 metered doses per canister	**Aerosol:** In 7.9 (institutional size) and 13g. canisters containing 60 and 120 metered doses respectively with propellants and with actuator. **Powder:.** In 4 blisters containing 15 rotadisks with inhalation device.	**Aerosol:** In 20g. inhaler (60mg triamcinolone acetonide) with actuator (≥240 metered doses)
Dosing	BID Note: Due to the smaller particle size of QVAR (an HFA product) the dose equivalent is ½ that of the former CFC beclomethasone products	BID – Turbuhaler QD-BID – Respules	BID	BID	TID-QID (may be given BID if double dose)
FDA labeled Indications	Maintenance and prophylactic treatment of asthma; includes patients who require systemic corticosteroids and may benefit from systemic dose reduction/elimination.				
Pediatric Labeling	• Qvar: ≥5 yoa	• Pulmicort Turbuhaler: ≥6 years of age • Pulmicort Respules: 12months- 8 yoa	• AeroBid, AeroBid-M: ≥6 yoa	• Flovent Rotadisk: ≥4 years of age • Flovent: ≥12 yoa	• Azmacort: ≥6 yoa
Other studied uses	• Chronic obstructive pulmonary disease (COPD) • Bronchopulmonary dysplasia (BPD) • Cystic fibrosis • Pulmonary sarcoidosis • Prevention of post-bronchiolitis wheezing				

Inhaled Corticosteroids					
Characteristic	**Qvar (beclomethasone)**	**Pulmicort Turbuhaler, Pulmicort Respules (budesonide)**	**AeroBid, AeroBid-M (flunisolide)**	**Flovent, Flovent Rotadisk (fluticasone)**	**Azmacort (triamcinolone)**
Contraindications/ Precautions	• Relief of acute bronchospasm; primary treatment of status asthmaticus or other acute episodes of asthma when intensive measures are required • Hypersensitivity to any ingredients. • Intranasal and inhaled corticosteroids may reduce growth in children; use the lowest effective dose; routinely monitor growth rate				
Drug interactions		Ketoconazole inhibits cP4503A4, thus increasing plasma levels of budesonide. Clinical significance unknown due to low systemic absorption of Pulmicort.		Ketoconazole inhibits cP4503A4, thus increasing plasma levels of fluticasone. Clinical significance unknown due to low systemic absorption of Flovent.	
Major Aes / Warnings	Suppression of HPA function, hoarseness, dry mouth, reduction in growth velocity				
Pharmacokinetics issues	None				

Inhaled Corticosteroids					
Characteristic	**Qvar (beclomethasone)**	**Pulmicort Turbuhaler, Pulmicort Respules (budesonide)**	**AeroBid, AeroBid-M (flunisolide)**	**Flovent, Flovent Rotadisk (fluticasone)**	**Azmacort (triamcinolone)**
Unique Features/Advantages	• HFA Inhaler • Non CFC • Smaller particle size allows for greater lung deposition (and thus efficacy of product)	• Breath actuated DPI Turbuhaler mat be easier for small children and the elderly to co-ordinate • Only corticosteroid nebulizer available	AeroBid-M has menthol flavoring	Rotadisk is breath actuated	Built in Spacer
	• There are two major delivery devices, the dry powdered inhaler (DPI) and the metered dose inhaler (MDI). The MDI requires appropriate technique to deliver the drug to lung tissues or use of a spacer device. The dry powder inhalers are free of additives and propellants, but the dry powder may act as an irritant. • The DPI system is breath activated and may be easier to use since less coordination is needed. This ease of use may reduce systemic absorption. Currently fluticasone and budesonide have DPI delivery systems. • Because of the possibility of higher systemic absoption, monitor patients using flunisolide for any evidence of systemic corticosteroid effect.				
Approximate dosage equivalents/ Summary/ Efficacy	The relative anti-inflammatory potency of inhaled corticosteroids are in the following order: Flunisolide = triamcinolone acetonide < beclomethasone diprprionate= budesonide < fluticasone. Current data only supports a difference in potency, not efficacy, among the inhaled corticosteroids; thus when used in equipotent dosages, efficacy is equal among all agents. The principle advantage of more potent inhaled corticosteroids may be in improved patient compliance and acceptance (less puffs per day) for those patients requiring higher dosages.				
Pipeline Agents/ Future Products	Flovent Diskus was approved September 29, 2000. A launch date has not yet been determined.				

Inhaled Corticosteroids Combinations	
Characteristic	**Advair Diskus (fluticasone propionate and salmeterol)**
Pharmacology	See pharmacology of individual agents
Generic formulation available?	No
Date of FDA Approval	August 24, 2000.
Manufacturer	GSK
Dosage forms / route of admin.	**Powder for inhalation**: 100 mcg fluticasone propionate, 50 mcg salmeterol 250 mcg fluticasone propionate, 50 mcg salmeterol 500 mcg fluticasone propionate, 50 mcg salmeterol all in 28 and 60 blisters in a disposable, purple-colored device.
Dosing	Adults and children 12 years of age: 1 inhalation twice daily (morning and evening, 12 hours apart). The maximum recommended dose of fluticasone propionate/salmeterol is 500 mcg/50 mcg twice daily.
FDA labeled indications	**Asthma, chronic:** For the long-term, twice-daily maintenance treatment of asthma in patients 12 years of age. Not indicated for the relief of acute bronchospasm.
Other studied uses	COPD
Contraindications	• Prior hypersensitivity to fluticasone or salmeterol • Acute bronchospasm • Status asthmaticus • IgE-mediated allergic reactions to lactose or milk products
Drug interactions	See individual agents
Major AEs / Warnings	Suppression of HPA function, hoarseness, dry mouth, reduction in growth velocity, tachycardia
Pharmacokinetics issues	None

Management of persistent symptoms in patients with asthma.
Lim KG.

Mayo Clin Proc. 2002 Dec;77(12):1333-8; quiz 1339.

Division of Pulmonary and Critical Care Medicine and Internal Medicine, Mayo Clinic, Rochester, Minn 55905, USA.

Abstract

The main goals of asthma therapy are to control symptoms, prevent acute attacks, and maintain lung function as close to normal as possible. Customizing the regimen to relieve the patient's symptoms and control airway inflammation is important. If asthma is not well controlled, an initial inhaled corticosteroid boost will treat the underlying heightened airway inflammation, and the addition of a long-acting beta2-adrenergic agonist or leukotriene receptor antagonist will rapidly control symptoms. Most patients do not require prolonged treatment with expensive combination or additive agents. Exercise-induced bronchoconstriction is a common source of symptoms. Treatments for scheduled and unscheduled exercises differ. Inhaled corticosteroids prevent frequent and severe asthma exacerbations. When patients have persistent symptoms despite a pharmacological regimen, environmental factors and nonpharmacological interventions must be considered before medication is increased. When an inhaled corticosteroid is being considered, issues of compliance, drug delivery device, and proper inhaler techniques are as important as issues of potency, clinical efficacy, and adverse effects. The new hydrofluoroalkane preparations offer more lung deposition and may be important in treating inflammation of the small airways in patients with asthma.

Establishing a therapeutic index for the inhaled corticosteroids: part I. Pharmacokinetic/pharmacodynamic comparison of the inhaled corticosteroids.

Kelly HW.

J Allergy Clin Immunol. 1998 Oct;102(4 Pt 2):S36-51.

College of Pharmacy and the Department of Pediatrics, University of New Mexico Health Sciences Center, Albuquerque 87131-1066, USA.

Abstract

The inhaled corticosteroids contain physicochemical differences that alter both glucocorticoid receptor-binding characteristics and the pharmacokinetic variables of these drugs. Differences in receptor-binding affinity translate into differences in potency for different drugs. Differences in pharmacokinetics, however, determine the topical effect to systemic effect ratio, or the "pulmonary targeting" of the drug. Beneficial pharmacokinetic properties that may improve pulmonary targeting include low oral bioavailability, rapid systemic clearance, and slow absorption from the lung. Delivery devices can produce clinically significant differences in topical activity by altering the dose deposited in the lung and, for orally absorbed drugs, the amount deposited in the oropharynx and swallowed. Clinical trials have confirmed that differences in potency or drug delivery of 2-fold or more can be detected in patients with asthma. However, because of the relatively flat nature of the dose-response curve for morning peak expiratory flow and forced expiratory volume in 1 second, the trials must be adequately powered and well controlled. The use of bronchial provocation measures are problematic because of the prolonged lag time for response. Study design flaws can lead to misinterpretation of results. Clinical studies have indicated the following relative potency differences: fluticasone propionate > budesonide = beclomethasone dipropionate > triamcinolone acetonide = flunisolide. Current evidence suggests that potency differences can be overcome by giving larger doses of the less potent drug. However, because of these potency differences, studies of systemic effects should not be done in isolation of adequate topical activity studies to define the pulmonary targeting of the drugs.

Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide (50/250 microg bd Diskus vs. formoterol (12 microg bd) and budesonide (800 microg bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma.

Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ; EDICT Investigators.
Respir Med. 2002 Nov;96(11):851-61.

Abstract
The aim of this study was to compare the efficacy safety and cost of Seretide (salmeterol/fluticasone propionate (Salm/FP), 50/250 microg bd) via Diskus with formoterol (Form; 12 microg bd) and budesonide (Bud; 800 microg bd) given concurrently (Form+Bud) via Turbuhaler in patients with moderate-to-severe asthma who were uncontrolled on existing corticosteroid therapy. The study used a randomised, double-blind, double-dummy, parallel-group design, consisting of a 2-week run-in period on current corticosteroid therapy (1000-1600 microg/day of BDP or equivalent) and a 12-week treatment period. Symptomatic patients (n = 428) with FEV1 of 50-85% predicted and increased symptom scores or reliever use during run-in were randomly allocated to receive either Salm/FP (50/250 microg bd) via a single Diskus inhaleror Form+Bud (12+800 microg bd) via separate Turbuhalers. Clinic, diary card and asthma-related health-care resource utilisation data were collected. Improvement in mean morning peak expiratory flow (PEFam was similar in the Salm/FP and Form+Bud groups. Both PEFam and mean evening PEF (PEFpm) increased by a clinically significant amount (>20 L/min) from baseline in both treatment groups. The mean rate of exacerbations (mild, moderate or severe) was significantly lower in the Salm/FP group (0.472) compared with the Form+Bud group (0.735) (ratio = 0.64; P < 0.001), despite the three-fold lower microgram inhaled corticosteroid dose in the Salm/FP group. Patients in the Salm/FP group also experienced significantly fewer nocturnal symptoms, with a higher median percentage of symptom-free nights (P = 0.04), nights with a symptom score <2 (P = 0.03), and nights with no awakenings (P = 0.02). Total asthma-related health-care costs were significantly lower in the Salm/FP group than the Form+Bud group (P<0.05). Both treatments were well tolerated, with a similar low incidence of adverse events. This study showed that in symptomatic patients with moderate-to-severe asthma, Salm/FP (50/250 microg bd), administered in a single convenient device (Diskus), was at least as effective as an approximately three-fold higher microgram corticosteroid dose of Bud (800 microg bd) given concurrently with Form (12 microg bd) in terms of improvement in PEFam, and superior at reducing exacerbations and nights with symptoms or night-time awakenings. Salm/FP was also the less costly treatment due primarily to lower hospitalization and drug costs.

Comparison of inhaled corticosteroids.
Kelly HW.

Ann Pharmacother. 1998 Feb;32(2):220-32.

College of Pharmacy, University of New Mexico Health Sciences Center, Albuquerque 87131, USA. hwkelly@unm.edu

Abstract

OBJECTIVE: To review the comparative studies evaluating both efficacy and safety of inhaled corticosteroids in the management of asthma. Specifically, comparative clinical trials are evaluated that allow clinicians to determine relative potencies of the various inhaled corticosteroids. METHODS: A critical review was performed of the published clinical trials, either as articles or abstracts, comparing the clinical efficacy or systemic activity of inhaled corticosteroids. No a priori criteria were applied, as this was not a meta-analysis. FINDINGS: In vitro measures of antiinflammatory activity of corticosteroids consistently demonstrate potency differences among the various corticosteroids. Traditionally, these in vitro measures have been used to develop new corticosteroids with greater topical activity. While no accepted direct measure of antiasthmatic antiinflammatory activity exists, clinical trials using surrogate measures (e.g., forced expiratory volume in 1 second, peak expiratory flow, bronchial hyperresponsiveness, symptom control) indicate that in vitro measures provide a relatively accurate assessment of antiasthmatic potency. The relative antiinflammatory potency of the inhaled corticosteroids is in the following rank order. flunisolide = triamcinolone acetonide < beclomethasone dipropionate = budesonide < fluticasone. Studies of systemic activity appear to confirm this relative order of potency. Currently, no evidence exists for greater efficacy for any of the inhaled corticosteroids when administered in their relative equipotent dosages. The preponderance of current data suggests that when administered in equipotent antiinflammatory doses as a metered-dose inhaler plus spacer or as their respective dry-powder inhaler, the existing inhaled corticosteroids have similar risks of producing systemic effects. CONCLUSIONS: Delivery systems can significantly affect both topical and systemic activity of inhaled corticosteroids. More direct comparative studies between agents are required to firmly establish comparative topical to systemic activity ratios. The preponderance of evidence suggests that the agents are not equipotent on a microgram basis.

Bronchodilator effect of an inhaled combination therapy with salmeterol + fluticasone and formoterol + budesonide in patients with COPD.

Cazzola M, Santus P, Di Marco F, Boveri B, Castagna F, Carlucci P, Matera MG, Centanni S.

Respir Med. 2003 May;97(5):453-7.

Department of Respiratory Medicine, A. Cardarelli Hospital, Unit of Pneumology and Allergology, Naples, Italy. mcazzola@qubisoft.it

Abstract

In the present trial, we compared the broncholytic efficacy of the combination therapy with 50 microg salmeterol + 250 microg fluticasone and 12 microg formoterol + 400 microg budesonide, both in a single inhaler device, in 16 patients with moderate-to-severe COPD. The study was performed using a single-blind crossover randomized study. Lung function, pulse oximetry (SpO2) and heart rate were monitored before and 15, 30, 60, 120, 180, 240, 300, 360, 480, 600, and 720 min after bronchodilator inhalation. Both combinations were effective in reducing airflow obstruction. FEV1 AUC(0-12 h) was 2.83 l (95% CI: 2.13-3.54) after salmeterol/fluticasone and 2.57 l (95% CI: 1.97-3.2) after formoterol/budesonide. Formoterol/budesonide elicited the mean maximum improvement in FEV1 above baseline after 120 min (0.29 l; 95% CI: 0.21-0.37) and salmeterol/fluticasone after 300 min (0.32 l; 95% CI: 0.23-0.41). At 720 min, the increase in FEV1 over baseline values was 0.10 l (95% CI: 0.07-0.12) after salmeterol/fluticasone and 0.10 l (95% CI: 0.07-0.13) after formoterol/budesonide. The mean peak increase in heart rate occurred 300 min after formoterol/budesonide (1.5 b/min; 95% CI--2.3 to 5.3) and 360 min after salmeterol/fluticasone (2.6 b/min; 95% CI--1.9 to 7.0). SpO2 did not change. All differences between salmeterol/fluticasone and formoterol/budesonide were not significant ($P > 0.05$) except those in FEV1 at 120 and 360 min. The results indicate that an inhaled combination therapy with a long-acting beta2-agonist and an inhaled corticosteroid appears to be effective in improving airway limitation after acute administration in patients suffering from COPD.

Adding formoterol to budesonide in moderate asthma--health economic results from the FACET study.

Andersson F, Stahl E, Barnes PJ, Lofdahl CG, O'Byrne PM, Pauwels RA, Postma DS, Tattersfield AE, Ullman A; Formoterol and Corticosteroid Establishing Therapy. International Study Group.

Respir Med. 2001 Jun;95(6):505-12.

AstraZeneca R&D Lund, Sweden. fredrik.l.andersson@astrazeneca.com

Abstract

The FACET (Formoterol and Corticosteroid Establishing Therapy) study established that there is a clear clinical benefit in adding formoterol to budesonide therapy in patients who have persistent symptoms of asthma despite treatment with low to moderate doses of an inhaled corticosteroid. We combined the clinical results from the FACET study with an expert survey on average resource use in connection with mild and severe asthma exacerbations in the U.K., Sweden and Spain. The primary objective of this study was to assess the health economics of adding the inhaled long-acting beta2-agonist formoterol to the inhaled corticosteroid budesonide in the treatment of asthma. The extra costs of adding the inhaled beta2-agonist formoterol to the corticosteroid budesonide in asthmatic patients in Sweden were offset by savings from reduced use of resources for exacerbations. For Spain the picture was mixed. Adding formoterol to low dose budesonide generated savings, whereas for moderate doses of budesonide about 75% of the extra formoterol costs could be recouped. In the U.K., other savings offset about half of the extra cost of formoterol. All cost-effectiveness ratios are within accepted cost-effectiveness ranges reported from previous studies. If productivity losses were included, there were net savings in all three countries, ranging from Euro 267-1183 per patient per year. In conclusion, adding the inhaled, long-acting beta2-agonist formoterol to low-moderate doses of the inhaled corticosteroid budesonide generated significant gains in all outcome measures with partial or complete offset of costs. Adding formoterol to budesonide can thus be considered to be cost-effective.

Antiasthmatics: Orally Inhaled Short-Acting Beta-2 Agonists				
Characteristic	**Proventil (albuterol)**	**Ventolin (albuterol)**	**Alupent (metaproterenol)**	**Maxair Autohaler (Pirbuterol)**
Pharmacology	Sympathomimetic agents are used to produce bronchodilation.They relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, bronchitis, emphysema, or bronchiectasis. Bronchodilation may additionally facilitate expectoration. The pharmacologic actions of these agents include: Alpha-adrenergic stimulation (vasoconstriction, nasal decongestion, pressor effects); ß$_1$-adrenergic stimulation (increased myocardial contractility and conduction); and ß$_2$-adrenergic stimulation (bronchial dilation and vasodilation, enhancement of mucociliary clearance, inhibition of cholinergic neurotransmission). Beta-adrenergic drugs stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3'5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Cyclic AMP that is formed inhibits the release of mediators of immediate hypersensitivity from inflammatory cells, especially from mast cellsand basophils. This increase of cyclic AMP leads to activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Other adrenergic actions include alpha receptor-mediated contraction of GI and urinary sphincters; a and ß receptor-mediated lipolysis; a and ß receptor-mediated decrease in GI tone; and changes in renin secretion, uterine relaxation, hepatic gylcogenolysis/gluconeogenesis, and pancreatic beta cell secretion. The relative selectivity of action of sympathomimetic agents is the primary determinant of clinical usefulness; it can predict the most likely side effects. ß$_2$ selective agents provide the greatest benefit with minimal side effects. Direct administration via inhalation provides prompt effects and minimizes systemic activity.			
Manufacturer	Schering	GlaxoSmithKline	Boehringer Ingelheim	3M Pharm.
FDA Approval Date	January 1, 1982	January 1, 1982	January 1, 1982	November 30, 1992
Generic formulation available?	Yes, except for HFA aerosol	Yes, except for HFA aerosol	No	No
Dosage forms / route of admin.	MDI HFA MDI	MDI HFA MDI	MDI	Autohaler (Breath Actuated)
Dosing frequency	Use prn for attacks 3-4 times daily or 15 mins before exercise for prophylaxis.	Use prn for attacks 3-4 times daily hours or 15 mins before exercise for prophylaxis.	Use 3-4 times daily.	Every 4 to 6 hours
General dosing guidelines	(Adults and children 12 years) Relief of bronchospasm, prevention of asthma symptoms: 1 to 2 inhalations every 4 to 6 hours. Prevention of exercise-induced bronchospasm: 2 inhalations 15 minutes before exercising.	Acute bronchospasm or asthma prevention: (Adults and children 4 years) 1 to 2 inhalations every 4 to 6 hours. Prevention of exercise-induced bronchospasm: (Adults and children 4 years) 2 inhalations 15 minutes before exercising.	(Adults) 2 to 3 inhalations no more than once every 3 to 4 hours; max 12 inhalations/day.	(Adults and children 12 years) Usually 2 inhalations every 4 to 6 hours. In some, 1 inhalation every 4 to 6 hours may suffice. Max 12 inhalations/day.
Pediatric labeling	12 years and up	4 years and up	12 years and up	12 years and up

Antiasthmatics: Orally Inhaled Short-Acting Beta-2 Agonists				
Characteristic	**Proventil (albuterol)**	**Ventolin (albuterol)**	**Alupent (metaproterenol)**	**Maxair Autohaler (Pirbuterol)**
Indications	Relief and prevention of bronchospasm. Prevention of exercise induced bronchospasm.		Treatment of bronchial asthma and reversible bronchospasm.	For prevention and reversal of bronchospasm in patients with reversible bronchospams including asthma.
Other studied uses	Treatment of hyperkalemia in hemodialysis. COPD, cardiogenic shock, Gamstorp's Syndrome. Gamstorp's Syndrome is adynamia episodica hereditaria (hyperkalaemic periodic paralysis) A form of periodic paralysis in which the serum potassium level is elevated during attacks; onset occurs in infancy, attacks are frequent but relatively mild, and myotonia is often present; autosomal dominant inheritance.		Exercise induced bronchospasm	
Contraindications	Hypersensitivity Hyperthyroidism, tachycardia or tachycardiac arrhythmias, or aortic stenosis		Hypersensitivity or tachycardia.	Hypersensitivity to pirbuterol or albuterol.
Drug interactions	Atomoxetine, MAOIs,Beta-blockers, TCAs Atomoxetine: Albuterol (600 mcg intravenously over 2 hours) induced increases in heart rate and blood pressure. Severity: Major. MAOIs: Adverse Effect: an increased risk of tachycardia, agitation, or hypomania. Severity: Major. Beta-Blockers: May inhibit cardiac, bronchodilating, and vasodilating effects. Severity: Major TCAs: Cardiovascular effects are potentiated (dysrhythmias have occurred). Severity: Major		MAOIs, Beta -blockers, TCAs MAOIs: Adverse Effect: an increased risk of tachycardia, agitation, or hypomania. Severity: Major. Beta-Blockers: May inhibit cardiac, bronchodilating, and vasodilating effects. Severity: Major TCAs: Cardiovascular effects are potentiated (dysrhythmias have occurred). Severity: Major	MAOIs, Beta-Blockers, TCAs MAOIs: Adverse Effect: an increased risk of tachycardia, agitation, or hypomania. Severity: Major. Beta-Blockers: May inhibit cardiac, bronchodilating, and vasodilating effects. Severity: Major TCAs: Cardiovascular effects are potentiated (dysrhythmias have occurred). Severity: Major
Major AEs / Warnings	Tachycardia, palpitations, GI upset, nausea. Caution in hyperthyroidism, diabetes, and CV disorders.			Nervousness, tremor, headache, palpitations. Caution in hyperthyroidism, diabetes, and CV disorders.
Pharmacokinetics issues	None	None	None	None

Antiasthmatics: Orally Inhaled Short-Acting Beta-2 Agonists				
Characteristic	**Proventil (albuterol)**	**Ventolin (albuterol)**	**Alupent (metaproterenol)**	**Maxair Autohaler (Pirbuterol)**
Dosage adjustment in key populations	Dosage reductions required for geriatric patients, hyperthyroidism, and in patients with CAD.		Initial dose in geriatric patients should be reduced.	None
Unique Features/Advantages	The duration of albuterol may be slightly longer than metaproterenol, however, metaproterenol may have a more rapid onset of action than albuterol. Many generic variations of albuterol are available. Proventil HFA and Ventolin HFA are MDIs propelled by hydrofluoralkane and are currently the only non-CFC non-powder inhaler alternative in this class.		The duration of albuterol may be slightly longer than metaproterenol, however, metaproterenol may have a more rapid onset of action than albuterol.	Pirbuterol has an Autohaler device that makes this product unique. Maxair Autohaler actuates upon inhalation.

National Asthma Education and Prevention Program Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.


Adobe.url

Inhaled short acting beta2-agonist use in chronic asthma: regular versus as needed treatment.

Walters EH, Walters J.
Cochrane Database Syst Rev. 2003;(2):CD001285.

Clinical School, University of Tasmania, Collins Street, Hobart, Tasmania, Australia.

Abstract

BACKGROUND: Inhaled short-acting beta-2 agonists are the major class of bronchodilators used for relief of symptoms in asthma. There has been concern that excessive uncontrolled use of beta-2 agonists might have contributed to rises in asthma mortality seen in some countries. International consensus guidelines now generally recommend using short-acting beta-2 agonists only for relief of symptoms on an as needed basis. OBJECTIVES: To assess the effects of using short-acting inhaled beta-2 agonists regularly or only on demand in asthmatic adults and children on indices of asthma control. SEARCH STRATEGY: Searches were carried out of the Cochrane Airways Group "Asthma and Wheez* RCT" register in 1997, 1999 and 2002. Pharmaceutical companies and researchers with an interest in the area were asked directly for details of any studies that they knew of. SELECTION CRITERIA: Randomised controlled trials in which the short-acting beta-2 agonist was given regularly in the experimental group, together with an inhaled bronchodilator for relief of symptoms ('rescue use'). The control group consisted of matching placebo inhaled regularly, with an inhaled bronchodilator for 'rescue use'. DATA COLLECTION AND ANALYSIS: Data were extracted and quality assessments were made by both reviewers. Parallel group and cross-over trials were analysed separately. Where possible data were pooled using a fixed effects model. MAIN RESULTS: 800 abstracts were identified for the first version and 60 papers were requested for full assessment. In this update 15 studies were added to the 34 trials which met the entry criteria for the first version in 2000. No clinically or statistically significant differences were found in airway calibre measurements. The regular treatment groups required less rescue medication, -0.80 puffs/24 hours (95% CI -0.07 to -1.30) and -0.42 puffs/daytime (95% CI -0.12 to -0.72), and had fewer days with asthma symptoms, -6.7% (95% CI -2.7 to -10.7). There was no significant difference in the odds ratio for the occurrence of at least one major asthma exacerbation either in parallel group or cross over studies. REVIEWER'S CONCLUSIONS: In general, these results support current guidelines, although it has given reassuring evidence against concerns over regular use of inhaled short-acting beta-2 agonists.

Inhaled Long-Acting Beta-Agonists		
Characteristic	**Serevent Diskus (salmeterol)**	**Foradil Aerolizer (formoterol)**
Pharmacology	Sympathomimetic agents are used to produce bronchodilation.They relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, bronchitis, emphysema, or bronchiectasis. Bronchodilation may additionally facilitate expectoration. The pharmacologic actions of these agents include: Alpha-adrenergic stimulation (vasoconstriction, nasal decongestion, pressor effects); ß$_1$-adrenergic stimulation (increased myocardial contractility and conduction); and ß$_2$-adrenergic stimulation (bronchial dilation and vasodilation, enhancement of mucociliary clearance, inhibition of cholinergic neurotransmission). Beta-adrenergic drugs stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3'5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Cyclic AMP that is formed inhibits the release of mediators of immediate hypersensitivity from inflammatory cells, especially from mast cellsand basophils. This increase of cyclic AMP leads to activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Other adrenergic actions include alpha receptor-mediated contraction of GI and urinary sphincters; a and ß receptor-mediated lipolysis; a and ß receptor-mediated decrease in GI tone; and changes in renin secretion, uterine relaxation, hepatic gylcogenolysis/gluconeogenesis, and pancreatic beta cell secretion. The relative selectivity of action of sympathomimetic agents is the primary determinant of clinical usefulness; it can predict the most likely side effects. ß$_2$ selective agents provide the greatest benefit with minimal side effects. Direct administration via inhalation provides prompt effects and minimizes systemic activity.	
Manufacturer	GlaxoSmithKline	Novartis
Date of FDA Approval	February 4, 1994 MDI discontinued in June 2003	February 16, 2001
Generic formulation available?	No	No
Dosage forms / route of admin.	50 mcg Diskus inhalation powder	12 mcg Gelatin capsules for inhalation
Dosing frequency	Every 12 hours	Every 12 hours

Inhaled Long-Acting Beta-Agonists		
Characteristic	**Serevent Diskus (salmeterol)**	**Foradil Aerolizer (formoterol)**
General Dosing Guidelines	(Adults and children 4 years) 1 inhalation (50mcg) twice daily (morning and evening, 12 hours apart). Exercise-induced bronchospasm: 1 inhalation 30 minutes before exercise, not more often than every 12 hours. COPD: 1 inhalation twice daily (morning and evening, 12 hours apart).	(Adults and children 5 years) Maintenance treatment of asthma: 1 capsule every 12 hours using Aerolizer Inhaler. (Adults and adolescents 12 years) Prevention of exercise-induced bronchospasm: 1 capsule inhaled 15 minutes before exercise; additional doses should not be used for 12 hours. Maintenance of COPD: 1 capsule inhaled every 12 hours. Max 24mcg/day.
Pediatric Labeling	4 years and up	5 years and up
Indications	Maintenance treatment of asthma and prevention of bronchospasm; Nocturnal asthma; Exercise Induced Bronchospasm (EIB); COPD	Maintenance treatment of asthma and prevention of bronchospasm; Nocturnal asthma; Exercise Induced Bronchospasm (EIB); COPD
Other studied uses	Cystic Fibrosis High-altitude pulmonary edema	
Contraindications	Hypersensitivity	Hypersensitivity
Drug interactions	MAOIs, Beta-blockers, TCAs, Diuretics, other sympathomimetics MAOIs: Adverse Effect: an increased risk of tachycardia, agitation, or hypomania. Severity: Major. Beta-Blocker: May inhibit cardiac, bronchodilating, and vasodilating effects. Severity: Major TCAs: Adverse Effect: an increased risk of cardiovascular excitation. Severity: Moderate. Diuretics: May add to effects of medications which deplete potassium (eg, loop or thiazide diuretics) Other sympathomimetics: May lead to to deleterious cardiovascular effects.	MAOIs, Beta-blockers, TCAs, methylxanthines, Diuretics, other sympathomimetics MAOIs: Adverse Effect: an increased risk of tachycardia, agitation, or hypomania. Severity: Major. Beta-Blocker: May inhibit cardiac, bronchodilating, and vasodilating effects. Severity: Major TCAs: Adverse Effect: an increased risk of cardiovascular excitation. Severity: Moderate. Methylxanthines: May potentiate hypokalemic effect. Diuretics: May add to effects of medications which deplete potassium (eg, loop or thiazide diuretics) Other sympathomimetics: May lead to to deleterious cardiovascular effects.
Major AEs / Warnings	Tremor, tachycardia, headache, sleep disturbance, agitation and tenseness are the most common side effects.	
Pharmacokinetics issues	None	None

Inhaled Long-Acting Beta-Agonists		
Characteristic	**Serevent Diskus (salmeterol)**	**Foradil Aerolizer (formoterol)**
Dosage adjustment in key populations	None	None
Unique Features/Advantages	Salmeterol is available as a DPI and in combination with fluticasone (Advair); formoterol is only available as a DPI. Long-acting inhaled beta-agonists are recommended in combination with corticosteroids for patients with moderate persistent asthma	Formoterol has a more rapid onset of action when compared to salmeterol; however, there is no difference in duration of effect between these agents. Available in a 12 µg capsule which is placed in an Aerolizer® inhaler, crushed and then inhaled, the device is easy to use and allows the patient or care-giver to assess whether the drug has been completely administered by visually checking the compartment after inhalation Long-acting inhaled beta-agonists are recommended in combination with corticosteroids for patients with moderate persistent asthma.

Comparative trough effects of formoterol and salmeterol on lymphocyte beta2-adrenoceptor--regulation and bronchodilatation.

Aziz I, McFarlane LC, Lipworth BJ.
Eur J Clin Pharmacol. 1999 Aug;55(6):431-6.

Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital and Medical School, University of Dundee, Scotland, UK.

Abstract

OBJECTIVES: The primary aim of the present study was to evaluate comparative trough effects of formoterol and salmeterol on beta2-adrenoceptor regulation and bronchodilator response after regular twice-daily treatment, with a secondary aim to evaluate any possible association with beta2-adrenoceptor polymorphism. METHODS: Sixteen asthmatic subjects, with mean (SD) age 33(9) years, all taking inhaled corticosteroids and with a forced expiratory volume in 1 s (FEV1) of 81(12)% predicted were recruited to take part in a randomised single-blind, three-way cross-over study. The subjects received three treatments each for 1 week, with 1-week washout periods in between: (1) formoterol dry powder, 12 microg twice daily, (2) salmeterol dry powder, 50 microg twice daily, or (3) placebo, twice daily. Spirometry and lymphocyte beta2-adrenoceptor parameters were measured before the first dose and 12 h after the last dose of each treatment, as well as domiciliary peak flow during each treatment. RESULTS: There were no differences in beta2-adrenoceptor density (Bmax) between the three treatments prior to the first dose; whereas, after the last dose, Bmax was lower with both active treatments than with placebo, but was significant for salmeterol only--a 1.2-fold geometric mean fold difference (95% CI 1- to 1.4-fold), P = 0.04. Compared with placebo, there were n = 9 of 16 subjects with salmeterol and n = 6 of 16 with formoterol who had a greater than 15% fall in Bmax. Post-hoc trend analysis of polymorphism showed that the propensity for downregulation appeared to be related to the occurrence of an allelic substitution of glycine at codon 16-8 of 13 for salmeterol versus 5 of 13 for formoterol with a greater than 15% fall compared with placebo. There were no significant differences between salmeterol and formoterol in terms of mean or individual values for downregulation. There was evidence of persistent bronchodilator activity with both active treatments compared with placebo; this was significant for forced expiratory flow rate between 25% and 75% of vital capacity (FEF25-75)--the mean difference versus salmeterol was 0.39 1/s (95% CI 0.06-0.70), P = 0.02, and versus formoterol was 0.35 1/s (95% CI 0.16-0.53), P = 0.001. These effects were mirrored by significant improvements in morning peak flow rate compared with placebo--mean difference versus salmeterol was 24 1/min (95% CI 7-42), P = 0.01, and versus formoterol was 36 1/min (95% CI 25-48), P < 0.0001. CONCLUSION: There were no differences between regular treatment with formoterol and salmeterol in their effects on lymphocyte beta2-adrenoceptor regulation at the end of a 12-h dosing interval, with both drugs exhibiting a residual degree of bronchodilator activity at the same time point. Further studies to evaluate receptor regulation and bronchodilator response are required in susceptible patients who have the homozygous glycine-16 polymorphism.

Cost-effectiveness analysis of formoterol versus salmeterol in patients with asthma.

Rutten-van Molken MP, van Doorslaer EK, Till MD.
Pharmacoeconomics. 1998 Dec;14(6):671-84.

Institute for Medical Technology Assessment, Erasmus University Rotterdam, The Netherlands. M.P.Rutten@econ.bmg.eur.nl

Abstract

OBJECTIVE: The aim of this study was to determine the relative economic consequences of treating asthmatics with twice daily dry powder formoterol 12 micrograms as compared with salmeterol 50 micrograms from a societal perspective. DESIGN AND SETTING: A randomised, 6-month, open-label study including 482 patients with asthma was conducted in Italy, Spain, France, Switzerland, the UK and Sweden. Medical costs included the costs of medications, physician services, emergency room visits, hospital admissions and lung function and other tests. Travel costs and costs of production loss were also calculated. Unit prices were estimated from external sources. To pool the costs of the 6 countries, European currencies were converted to US dollars using 1995 exchange rates. Outcome measures were the number of episode-free days (EFDs) and the number of patients reaching a clinically relevant improvement in quality of life as measured using the St. Georges Respiratory Questionnaire. MAIN OUTCOME MEASURES AND RESULTS: There were no significant differences between the 2 treatment arms in the frequency of emergency room visits, hospital admissions, use of rescue medication or contacts with general practitioners (GPs), specialists or nurses. Median medical costs over 6 months were $US828 per patient with formoterol and $US850 with salmeterol. This difference was not statistically significant. In both groups, about 60% of all days were episode-free. Average costs per EFD were about $US9 for both treatments. The average cost per patient reaching a clinically relevant improvement in quality of life was between $US1300 and $US1400. Incremental cost-effectiveness ratios were not calculated because both costs and outcomes were not significantly different. Asthma-related absenteeism ranged between 3 days and 6 months per patient in both groups. CONCLUSIONS: There was no evidence to suggest that either treatment was more cost effective than the other.

Salmeterol versus formoterol in patients with moderately severe asthma: onset and duration of action.

van Noord JA, Smeets JJ, Raaijmakers JA, Bommer AM, Maesen FP.
Eur Respir J. 1996 Aug;9(8):1684-8.

Dept of Respiratory Diseases, De Wever Hospital, Heerlen, The Netherlands.

Abstract

We evaluated the profile of the bronchodilatory effect of three inhaled beta2-agonists, 24 microg formoterol, 50 microg salmeterol and 200 microg salbutamol, in patients with stable, moderately severe asthma. Thirty asthmatics (mean+/-SD age 54+/-8 yrs; forced expiratory volume in one second (FEV1) 58+/-12% predicted; reversibility of FEV1 21+/-8% from baseline) participated in a single-centre, double-blind, randomized, single-dose, cross-over study. FEV1 was obtained in baseline condition and 10, 20, 30, 60 min, and every hour up to 12 h after inhalation of the trial drug. Specific airway conductance (sGaw) was measured at baseline condition and 1, 3, 5, 7, 10, 20, 30, 60 min, and every hour up to 12 h after inhalation. Formoterol produced a mean increase in sGaw (as % of baseline) of 44% after 1 min, maximal (135%) after 2 h, and 56% after 12 h. The mean increase in FEV1 was maximal (27%) after 2h, and 10% after 12 h. After salmeterol, mean increase in sGaw amounted to 16% after 3 min, maximal (111%) after 2-4 h, and 58% after 12 h. The mean increase in FEV1 was maximally 25% after 3h, being 11% after 12 h. After salbutamol, mean increase in sGaw was 44% after 1 min and maximal (100%) after 30 min. The peak increase in FEV1 was 25%. We conclude that formoterol (24 microg) and salmeterol (50 microg) had an equal bronchodilatory capacity, which was similar to that of 200 microg salbutamol and lasted for at least 12 h in patients with asthma. However, formoterol had a more rapid onset of action than salmeterol, equal to that of salbutamol.

Antiasthmatics: Short-Acting Beta-2 Agonist Nebulizers				
Characteristic	**AccuNeb (Albuterol)**	**Proventil (Albuterol)**	**Xopenex (Levalbuterol)**	**Alupent (Metaproterenol)**
Pharmacology	Sympathomimetic agents are used to produce bronchodilation.They relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, bronchitis, emphysema, or bronchiectasis. Bronchodilation may additionally facilitate expectoration. The pharmacologic actions of these agents include: Alpha-adrenergic stimulation (vasoconstriction, nasal decongestion, pressor effects); ß$_1$-adrenergic stimulation (increased myocardial contractility and conduction); and ß$_2$-adrenergic stimulation (bronchial dilation and vasodilation, enhancement of mucociliary clearance, inhibition of cholinergic neurotransmission). Beta-adrenergic drugs stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3'5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Cyclic AMP that is formed inhibits the release of mediators of immediate hypersensitivity from inflammatory cells, especially from mast cellsand basophils. This increase of cyclic AMP leads to activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Other adrenergic actions include alpha receptor-mediated contraction of GI and urinary sphincters; a and ß receptor-mediated lipolysis; a and ß receptor-mediated decrease in GI tone; and changes in renin secretion, uterine relaxation, hepatic gylcogenolysis/gluconeogenesis, and pancreatic beta cell secretion. The relative selectivity of action of sympathomimetic agents is the primary determinant of clinical usefulness; it can predict the most likely side effects. ß$_2$ selective agents provide the greatest benefit with minimal side effects. Direct administration via inhalation provides prompt effects and minimizes systemic activity. Note: Levalbuterol is the R(-)-enantiomer of racemic albuterol.			
Manufacturer (if single source)	Dey	Available generically	Sepracor	Available generically
FDA Approval Date	April 30, 2001	January 14, 1987	March 25, 1999	June 30, 1983
Generic formulation available?	No	Yes	No	Yes
Dosage forms / route of admin.	0.63mg/3ml and 1.25mg/3ml nebulizer solution preservative free	0.083%, 3ml UD vials 0.5%, 20 ml container with dropper nebulizer solution	0.31, 0.63, and 1.25mg/3ml nebulizer solution Preservative-free. Sulfuric acid. In UD 3 mL vials.	5% nebulizer solution in 10ml and 30 ml w/dropper may contain EDTA& benzalkonium chloride 0.4%, 0.6% solution for nebulization in 2.5ml UD vials, may contain EDTA & benzalkonium chloride
Dosing frequency	Use 3-4 times daily	Use 3-4 times daily	Every 6-8 hours	Use 3-4 times daily

Antiasthmatics: Short-Acting Beta-2 Agonist Nebulizers				
Characteristic	**AccuNeb (Albuterol)**	**Proventil (Albuterol)**	**Xopenex (Levalbuterol)**	**Alupent (Metaproterenol)**
General dosing guidelines	The usual starting dosage for patients 2 to 12 years of age is 1.25 mg or 0.63 mg administered 3 or 4 times/day, as needed, by nebulization. More frequent administration is not recommended. Deliver over 5 to 15 minutes. AccuNeb has not been studied in the setting of acute attacks of bronchospasm.	Adults and children 12 years of age: 2.5 mg 3 to 4 times/day by nebulization. Dilute 0.5 mL of the 0.5% solution with 2.5 mL sterile normal saline. Deliver over 5 to 15 minutes. Children 2 to 12 years of age (15 kg): 2.5 mg (1 UD vial) 3 to 4times/day by nebulization. Children weighing < 15 kg who require <2.5mg/dose (ie, less than a full UD vial) should use the 0.5% inhalation solution. Deliver over 5 to 15 minutes.	(Adults, adolescents 12 years) Start at 0.63mg three times daily by nebulization. May increase to 1.25mg three times daily if needed, tolerated. (Children 6 to 11 years) 0.31mg three times daily by nebulization. Max 0.63mg three times daily.	Usually, treatment does not need to be repeated more often than every 4 hours to relieve acute bronchospasm attacks. In chronic bronchospastic pulmonary diseases, give 3 to 4times/day. A single dose of nebulized metaproterenol in the treatment of an acute attack of asthma may not completely abort an attack. Not recommended for children < 12 years of age. Administer the unit-dose vial by oral inhalation using an intermittent positive pressure breathing (IPPB) device. The usual adult dose is 1vial per nebulization treatment. Each 0.4%vial is equivalent to 0.2 mL of the 5% solution diluted to 2.5 mL with normal saline. Each 0.6%vial is equivalent to 0.3 mL of the 5% solution diluted to 2.5 mL with normal saline.
Pediatric Labeling	2 years and up	2 years and up	6 years and up	12 years and up
Indications	Relief and prevention of bronchospasm. Prevention of exercise induced bronchospasm.	Relief and prevention of bronchospasm. Prevention of exercise induced bronchospasm.	Relief and prevention of bronchospasm.	Treatment of bronchial asthma and reversible bronchospasm.

Antiasthmatics: Short-Acting Beta-2 Agonist Nebulizers				
Characteristic	**AccuNeb (Albuterol)**	**Proventil (Albuterol)**	**Xopenex (Levalbuterol)**	**Alupent (Metaproterenol)**
Other studied uses	Treatment of hyperkalemia in hemodialysis. COPD, cardiogenic shock, Gamstorp's Syndrome. Gamstorp's Syndrome is adynamia episodica hereditaria (hyperkalaemic periodic paralysis) A form of periodic paralysis in which the serum potassium level is elevated during attacks; onset occurs in infancy, attacks are frequent but relatively mild, and myotonia is often present; autosomal dominant inheritance.		None	Exercise induced bronchospasm
Contraindications	Hyperthyroidism, tachycardia or tachycardiac arrhythmias, or aortic stenosis	Hyperthyroidism, tachycardia or tachycardiac arrhythmias, or aortic stenosis	Hypersensitivity to levalbuterol or albuterol	Hypersensitivity or tachycardia.
Drug interactions	Atomoxetine, MAOIs,Beta-blockers, TCAs Atomoxetine: Albuterol (600 mcg intravenously over 2 hours) induced increases in heart rate and blood pressure. Severity: Major. MAOIs: Adverse Effect: an increased risk of tachycardia, agitation, or hypomania. Severity: Major. Beta-Blockers: May inhibit cardiac, bronchodilating, and vasodilating effects. Severity: Major TCAs: Cardiovascular effects are potentiated (dysrhythmias have occurred). Severity: Major	Atomoxetine, MAOIs,Beta-blockers, TCAs Atomoxetine: Albuterol (600 mcg intravenously over 2 hours) induced increases in heart rate and blood pressure. Severity: Major. MAOIs: Adverse Effect: an increased risk of tachycardia, agitation, or hypomania. Severity: Major. Beta-Blockers: May inhibit cardiac, bronchodilating, and vasodilating effects. Severity: Major TCAs: Cardiovascular effects are potentiated (dysrhythmias have occurred). Severity: Major	MAOIs, Beta-blockers, digoxin, and diuretics. MAOIs: Adverse Effect: an increased risk of tachycardia, agitation, or hypomania. Severity: Major. Beta-Blockers: May inhibit cardiac, bronchodilating, and vasodilating effects. Severity: Major Digoxin: Digoxin levels may be decreased. Severity: minor. Diuretics: May add to effects of medications which deplete potassium (eg, loop or thiazide diuretics)	MAOIs, Beta -blockers, TCAs MAOIs: Adverse Effect: an increased risk of tachycardia, agitation, or hypomania. Severity: Major. Beta-Blockers: May inhibit cardiac, bronchodilating, and vasodilating effects. Severity: Major TCAs: Cardiovascular effects are potentiated (dysrhythmias have occurred). Severity: Major

Antiasthmatics: Short-Acting Beta-2 Agonist Nebulizers				
Characteristic	**AccuNeb (Albuterol)**	**Proventil (Albuterol)**	**Xopenex (Levalbuterol)**	**Alupent (Metaproterenol)**
Major AEs / Warnings	Tachycardia, palpitations, GI upset, nausea. Caution in hyperthyroidism, diabetes, and CV disorders.			

Antiasthmatics: Short-Acting Beta-2 Agonist Nebulizers				
Characteristic	**AccuNeb (Albuterol)**	**Proventil (Albuterol)**	**Xopenex (Levalbuterol)**	**Alupent (Metaproterenol)**
Pharmacokinetics issues	None	None	None	None
Dosage adjustment in key populations	Dosage reductions required for geriatric patients, hyperthyroidism, and in patients with CAD.	Dosage reductions required for geriatric patients, hyperthyroidism, and in patients with CAD.	Initial dose in geriatric patients should be reduced.	Initial dose in geriatric patients should be reduced.
Unique Features/Advantages Summary	Accuneb is only available in nebulizer solution that is preservative free.	The duration of albuterol may be slightly longer than metaproterenol, however, metaproterenol may have a more rapid onset of action than albuterol. Many generic variations of albuterol are available.	Levalbuterol is only available in nebulizer solution.	The duration of albuterol may be slightly longer than metaproterenol, however, metaproterenol may have a more rapid onset of action than albuterol.
	Safety and Efficacy Trials of Albuterol versus Levalbuterol follow			

The safety and efficacy of nebulized levalbuterol compared with racemic albuterol and placebo in the treatment of asthma in pediatric patients.

Gawchik SM, Saccar CL, Noonan M, Reasner DS, DeGraw SS.
J Allergy Clin Immunol. 1999 Apr;103(4):615-21.

Supported by Sepracor
Asthma and Allergy Research Associates, Chester, PA 19013, USA.

BACKGROUND: Limited dose-response information is available for nebulized beta2 -agonists, especially in young children. OBJECTIVE: The purpose of this study was to determine the safety and efficacy of increasing doses of nebulized levalbuterol (Xopenex; the pure R-isomer of racemic albuterol) and racemic albuterol compared with placebo in the treatment of asthma in pediatric patients. METHODS: In this randomized, double-blind, crossover study, children (aged 3 to 11 years) with asthma (resting FEV1 50% to 80% of predicted normal [Polgar's] values) were treated with either levalbuterol, racemic albuterol, or placebo. Eligible subjects underwent a screening visit followed by 4 treatment visits. At each treatment visit, serial pulmonary function tests were completed before and after the treatment; plasma was collected to determine enantiomer levels, and safety was evaluated. RESULTS: Five 3- to 5-year-old patients and twenty-eight 6- to 11-year-old patients completed the study, and a total of 87 doses of levalbuterol were administered. In the 6- to 11-year-old group, all doses of levalbuterol were significantly greater than placebo in peak change and percent peak change in FEV1 and area under the FEV1 versus time curve (P <.05). The FEV1 values over the 8-hour study period were similar for levalbuterol 0.31 and 0.63 mg and racemic albuterol 2.5 mg and were greatest after levalbuterol 1.25 mg. Median plasma levels of R-albuterol depended on dose and were 0.4, 0.7, 1.2, and 1.0 after levalbuterol 0.31 mg, 0.63 mg, and 1.25 mg and racemic albuterol 2.5 mg, respectively. All patients in the 2.5-mg racemic albuterol arm had measurable plasma levels of S-albuterol, although S-albuterol levels were undetectable in most patients in the levalbuterol arms. In a few patients who received levalbuterol, S-albuterol levels were detected, which was likely because of the use of racemic albuterol as a concomitant medication. All active treatments were well tolerated. beta-Mediated changes in heart rate, potassium, and glucose were dose dependent for all active treatment groups. CONCLUSION: Levalbuterol caused a significantly greater increase in FEV1 than placebo, and FEV1 values were comparable with or better than those observed with racemic albuterol. beta-Mediated side effects were lower for an equipotent dose of levalbuterol when compared with racemic albuterol. Treatment with levalbuterol resulted in plasma levels that were dose dependent and had an approximate correlation with pharmacodynamic parameters.

Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma.

Nelson HS, Bensch G, Pleskow WW, DiSantostefano R, DeGraw S, Reasner DS, Rollins TE, Rubin PD.

Supported by Sepracor
J Allergy Clin Immunol. 1998 Dec;102(6 Pt 1):943-52.

National Jewish Medical and Research Center, Denver, CO, USA.

BACKGROUND: Racemic albuterol is an equal mixture of (R)-albuterol (levalbuterol), which is responsible for the bronchodilator effect, and (S)-albuterol, which provides no benefit and may be detrimental. OBJECTIVE: We sought to compare 2 doses of a single enantiomer, levalbuterol (0.63 mg and 1.25 mg), and equivalent amounts of levalbuterol administered as racemic albuterol with placebo in patients with moderate-to-severe asthma. METHODS: This was a randomized, double-blind, parallel-group trial. Three hundred sixty-two patients 12 years of age or older were treated with study drug administered by means of nebulization 3 times daily for 28 days. The primary endpoint was peak change in FEV1 after 4 weeks. RESULTS: The change in peak FEV1 response to the first dose in the combined levalbuterol group was significantly greater compared with the combined racemic albuterol group (0.92 and 0.82 L, respectively; P =.03), with similar but nonsignificant results after 4 weeks (0.84 and 0.74 L, respectively). Improvement in FEV1 was similar for levalbuterol 0.63 mg and racemic albuterol 2.5 mg and greatest for levalbuterol 1.25 mg. Racemic albuterol 1.25 mg demonstrated the weakest bronchodilator effect, particularly after chronic dosing. The greatest increase in FEV1 was seen after levalbuterol 1.25 mg, especially in subjects with severe asthma. All active treatments were well tolerated, and beta-adrenergic side effects after administration of levalbuterol 0.63 mg were reduced relative to levalbuterol 1.25 mg or racemic albuterol 2.5 mg. At week 4, the predose FEV1 value was greatest in patients who received levalbuterol or placebo when compared with those who received racemic albuterol. The difference was more evident and was statistically significant in patients who were not receiving inhaled corticosteroids. CONCLUSION: Levalbuterol appears to provide a better therapeutic index than the standard dose of racemic albuterol. These results support the concept that (S)-albuterol may have detrimental effects on pulmonary function.

Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol.

Milgrom H, Skoner DP, Bensch G, Kim KT, Claus R, Baumgartner RA; Levalbuterol Pediatric Study Group.

J Allergy Clin Immunol. 2001 Dec;108(6):938-45.

Supported by Sepracor

National Jewish Medical and Research Center, Denver, Colorado, USA.

BACKGROUND: Racemic albuterol (RAC) is an equal mixture of (R)-albuterol and (S)-albuterol. Only the (R)-isomer, levalbuterol (LEV), is therapeutically active. Lower doses of LEV, devoid of (S)-albuterol, have demonstrated efficacy comparable to that of higher doses of the (R)-isomer administered as a component of RAC. OBJECTIVE: The purpose of this study was to determine whether LEV results in improved safety and efficacy in children. METHODS: Asthmatic children aged 4 to 11 years (n = 338; FEV(1), 40% to 85% of predicted) participated in this multicenter, randomized, double-blinded study and received 21 days of 3-times-a-day treatment with nebulized LEV (0.31 or 0.63 mg), RAC (1.25 or 2.5 mg), or placebo. The primary endpoint was FEV(1) (peak percent change). Adverse events, clinical laboratory test results, vital signs, and electrocardiograms were evaluated for safety. RESULTS: All active treatments significantly improved the primary endpoint in comparison with placebo ($P < .001$). Significant differences in FEV(1) were noted immediately after nebulization (median change, 2.0%, 19.0%, 18.1%, 12.4%, and 15.6% for placebo, LEV 0.31 and 0.63, RAC 1.25 and 2.5 mg, respectively; $P < .05$ vs placebo; $P < .05$ for LEV 0.31 and 0.63 vs RAC 1.25 mg). LEV 0.31 mg was the only treatment not different from placebo for changes in ventricular heart rate, QT(c) interval, and glucose ($P > .05$). All active treatments decreased serum potassium (range, -0.3 to -0.6; $P < .002$ vs placebo), and RAC 2.5 mg caused the greatest change ($P < .005$ vs other actives). In a patient subset with severe asthma, a dose-response relationship was observed for levalbuterol, indicating that higher doses were more effective. CONCLUSION: LEV was clinically comparable to 4- to 8-fold higher doses of RAC, and it demonstrated a more favorable safety profile. LEV 0.31 mg should be used as the starting dose in 4-11 year old children with mild to moderate persistent asthma. Patients with severe disease might benefit from higher doses.

The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients.

Lotvall J, Palmqvist M, Arvidsson P, Maloney A, Ventresca GP, Ward J.
J Allergy Clin Immunol. 2001 Nov;108(5):726-31.

Supported by GlaxoSmithKline
Department of Respiratory Medicine and Allergology, Goteborg University, Goteborg, Sweden.

BACKGROUND: It has been suggested that R-albuterol produces bronchodilation that is comparable with that of racemic albuterol (RS-albuterol) on a 4:1 dose-for-dose basis but systemic side effects on a 2:1 basis, implying better therapeutic ratio for R-albuterol. OBJECTIVE: We sought to carefully compare the bronchodilating and systemic effects of R- and RS-albuterol by using a crossover study design. METHODS: Twenty asthmatic patients (15.1%-28.7% FEV(1) reversibility) were given R-albuterol (6.25-1600 microg), S-albuterol (6.25-1600 microg), RS-albuterol (12.5-3200 microg), or placebo in a crossover, double-blind, placebo-controlled fashion. Cumulative doses were given with a Mefar dosimeter, and FEV(1), heart rate, and plasma K(+) levels were measured 20 minutes after each dose. RESULTS: Both R- and RS-albuterol produced dose-related improvement in FEV(1) and, at higher doses, increased heart rate and decreased plasma K(+) levels. Neither placebo nor S-albuterol had any significant effect. Individual estimates of the potency ratio for R-albuterol/RS-albuterol were calculated and summarized across all subjects. The geometric mean potency ratio for effects on FEV(1) was 1.9 (95% CI, 1.3-2.8), on HR of 1.9 (95% CI, 1.3-2.9), and on K(+) level of 1.7 (95% CI, 1.3-2.1). CONCLUSION: All pharmacologic effects of RS-albuterol reside with the R-enantiomer, and S-albuterol is clinically inactive. The R-albuterol/RS-albuterol potency ratios for local (FEV(1)) and systemic effects (heart rate and K(+)) are similar, suggesting a comparable therapeutic ratio for R-albuterol and RS-albuterol in asthmatic subjects.

Levalbuterol nebulizer solution: is it worth five times the cost of albuterol?

Asmus MJ, Hendeles L.
Pharmacotherapy. 2000 Feb;20(2):123-9.

Supported by Dey
Department of Pharmacy Practice, College of Pharmacy, University of Florida, Gainesville, USA.

Albuterol is a 50:50 mixture of R-albuterol, the active enantiomer, and S-albuterol, which appears to be inactive in humans. The Food and Drug Administration recently approved levalbuterol, the pure R-isomer, as a preservative-free nebulizer solution. Published studies indicate that it is neither safer nor more effective than an equimolar dose of racemic albuterol (levalbuterol 1.25 mg = albuterol 2.5 mg). However, these studies were conducted in patients with stable asthma (at the top of the dose-response curve), whereas a nebulized bronchodilator most likely would be used by patients with an acute exacerbation. Because such patients, in the hospital setting, often require higher doses of albuterol, the manufacturer's recommended dose of levalbuterol is likely to be too low for rescue therapy. Levalbuterol may cost as much as 5 times more than racemic albuterol, depending on purchase method. We conclude that levalbuterol offers no advantage over albuterol but is likely to be more costly.

Levalbuterol and racemic albuterol: Are there therapeutic differences?

Richard Ahrens MD
Miles Weinberger MD

Journal of Allergy and Clinical Immunology
Volume 108 • Number 5 • November 2001

From the Pediatric Allergy and Pulmonary Division, University of Iowa College of Medicine.
Received for publication August 7, 2001.

J Allergy Clin Immunol 2001;108:681-4.

In a 1998 report in the JACI, Nelson et al[1] concluded that levalbuterol (the generic name for R-albuterol administered as a single enantiomer) had a better therapeutic ratio than racemic albuterol (which contains both the R- and S-enantiomers of albuterol). The following year, Gawchik et al[2] likewise concluded that levalbuterol had fewer ß-agonist–mediated side effects than racemic albuterol when administered in doses that produce similar efficacy. Handley et al[3] also reported that nebulized levalbuterol, in doses yielding comparable bronchodilation, had fewer ß-agonist–mediated side effects than nebulized racemic albuterol (R,S-albuterol). All 3 reports implied that levalbuterol had a therapeutic advantage over racemic albuterol because less R-albuterol was required to produce the same degree of efficacy when administered as levalbuterol than when administered in a racemic formulation. Negative effects of the Senantiomer were proposed as the explanation for this. The lower dose of R-albuterol (levalbuterol), in turn, resulted in fewer systemic effects for the same degree of bronchodilator efficacy (ie, a better “therapeutic ratio”).

However, in a report appearing in this month's issue of the Journal, Lötvall et al[4] arrived at a different conclusion. They failed to find any difference between the therapeutic ratios for levalbuterol and the racemic formulation. Specifically, they found that all pharmacologic effects of racemic albuterol reside with levalbuterol (the R-enantiomer) and that the S-albuterol was clinically inactive. Why the difference, and which conclusion should guide therapeutic decision-making?

Concerns about potential adverse effects of S-albuterol were first supported by results obtained from preclinical animal and in vitro models .[5] [7] These studies, previously reviewed in the pages of this Journal,[8] [10] indicated that S-albuterol had proinflammatory effects, increased airway smooth muscle responsiveness to LTC4 and histamine, and acted in opposition to the airway protective effects of R-albuterol (levalbuterol) against antigen-induced bronchospasm.

On the basis of these preclinical studies, clinically relevant adverse effects of S-albuterol in human beings were postulated.[10] These included the following: diminution of the efficacy of R,S-albuterol by working in opposition to the bronchodilator and bronchoprotective effects of R-albuterol; the development of tolerance to beneficial effects of R,S-albuterol with repeated use, based on the preferential accumulation of S-albuterol versus R-albuterol in the lung; increased airway responsiveness, possibly due to proinflammatory effects of S-albuterol; and the potential for producing paradoxical bronchospasm. The potential for these clinically important adverse effects from S-albuterol provided the rationale for clinical development of a nebulized formulation of relatively pure R-albuterol (levalbuterol) and its marketing under the trade name Xopenex.

Because the conclusions of Lötvall et al[4] in this issue of the Journal conflict with those in the other publications noted above,[1] [3] it is appropriate to reexamine the weight of evidence from all of the published clinical trials that have attempted to test the hypothesized adverse effects of S-albuterol and the associated potential benefits of using levalbuterol rather than racemic albuterol.

Hypothesis: S-albuterol works in opposition to the bronchodilator and bronchoprotective effects of R-albuterol
If true in human beings, this adverse effect of S-albuterol would cause R-albuterol, administered as levalbuterol, to be significantly more potent than an equal amount of R-albuterol given in the racemic formulation. Let us first look

in more detail at the studies whose conclusions supported this hypothesis. The study by Nelson et al evaluated the bronchodilator effects of the levalbuterol and racemic formulations in 362 adolescent and adult subjects treated with levalbuterol, racemic albuterol, or placebo 3 times daily for 4 weeks. Two doses of each formulation were given: 630 and 1250 µg of levalbuterol and 1250 and 2500 µg of the racimate. These doses were matched to deliver the same quantities of R-albuterol (ie, 630 and 1250 µg). The mean peak change in FEV1 from baseline that occurred with the active regimens ranged from approximately 35% to 42%. Given the mean baseline FEV1 of approximately 60% of predicted, this is consistent with postbronchodilator values that differed very little, averaging from approximately 81% to 85% of predicted for each of the active regimens. Although the mean differences between active regimens were small, a statistically significant difference was found between levalbuterol and the racemic preparation after the first dose, though not after 4 weeks of 3-times-a-day treatment.

In a study of 43 children, Gawchik et al[2] compared 4 single doses of levalbuterol, ranging from 160 to 1250 µg, with 1250- and 2500-µg doses of the racemic formulation. Although all regimens provided a significant bronchodilator effect in comparison with placebo, no significant difference in bronchodilator effect could be demonstrated between any of the active regimens.

The report of Handley et al[3] compared several doses of levalbuterol, ranging from 310 to 1250 µg, with a 2500-µg dose of the racemic formulation. No significant differences between active regimens were reported among the 20 adult subjects.

Authors of all 3 of these studies[1] [3] found similar bronchodilatation for the 630-µg dose of levalbuterol and the 2500-µg dose of racemic albuterol. This has been taken to indicate that levalbuterol as the single enantiomer has a better therapeutic index by being more effective and having less potential for adverse effects in the absence of the S-enantiomer.

However, none of these studies provides strong support for the hypothesis that R-albuterol is more potent when administered as levalbuterol than when administered in the racemic formulation. In fact, the results of each of these studies violate the basic validity criteria that apply to investigations intended to compare the potencies of formulations.[12] [13] Such violation occurs in more than one way, but the most important is this: none of these studies was able to demonstrate a significant dose-response relationship. Stated another way: If these studies cannot detect differences between different doses of the same formulation, then they clearly are inadequate to evaluate and quantitate differences between different formulations.

Rigorous methods for comparing and estimating differences in potency of inhaled ß-agonist formulations have been published.[12] [14] [16] These methods use bioassay study design and statistical analyses to estimate differences in potency and are capable of making such estimates with a high degree of precision. The study by Lötvall et al,[4] reported in this issue of the Journal, is the first to use statistical bioassay methodology to estimate the relative potency of levalbuterol and racemic albuterol. The authors examined the results of progressively increasing doses of R- or S-albuterol ranging from 625 to 3200 µg as the individual enantiomers and combined in the racemic formulation. The potency ratio that they calculated for R- versus R,S-albuterol was 1.9, indicating that each microgram of levalbuterol was equivalent to 1.9 µg of racemic albuterol. The 95% CI encompassed a relative potency of 2, as would be expected if all pharmacologic effects of racemic albuterol were entirely from the R-enantiomer. In other words, the pharmacologic activity of the Renantiomer was the same when the single enantiomer (levalbuterol) was used as when the S-enantiomer was also present, as in the racemic formulation. Although this study can be criticized for using a cumulative-dose design, which confounds the effects of time and dosing,[17] the authors' approach nonetheless provides the most reliable estimates of differences in potency between levalbuterol and racemic albuterol available to date.

Several other studies that have tested this hypothesis using albuterol-induced protection against methacholine challenge. Perrin-Fayolle,[18] in a brief report published as a letter in The Lancet, described enhanced protection against methacholine challenge when levalbuterol (identified as D-salbutamol in the report) was administered as the single enantiomer in comparison with racemic albuterol and reported that S-salbutamol (identified as L-salbutamol in the report) increased airway sensitivity to methacholine. However, the differences observed between levalbuterol and the racemic formulation were not statistically significant, and others have failed to find any evidence of a difference in bronchoprotective or bronchodilator effect between R-albuterol given alone and R-albuterol given at the equivalent dose in the racemic formulation.[19] [20]

The weight of evidence thus supports neither the concept that S-albuterol works in opposition to the bronchodilator and bronchoprotective effects of R-albuterol nor the concept that there is any difference in R-albuterol potency when it is administered as a single enantiomer rather than in a racemic formulation.

Hypothesis: S-albuterol is responsible for development of tolerance to the beneficial effects of R,S-albuterol
If true in human beings, this would cause the tolerance after repeated administration of levalbuterol to be absent or at least smaller in magnitude than that associated with racemic albuterol. Only a study by Cockcroft et al[21] addresses this hypothesis. They administered R-albuterol alone, S-albuterol alone, racemic albuterol (all enantiomers in equimolar doses), or placebo for 6 days. On days 0 and 7, they evaluated the protective effect of the R-albuterol on methacholine responsiveness. They found a significant and equivalent degree of tolerance after R-albuterol and racemic albuterol treatment but not after S-albuterol or placebo treatment. This does not support the hypothesis that S-albuterol is involved in the induction of tolerance to bronchoprotective effects of albuterol and argues against the suggestion that less tolerance develops when R-albuterol is administered as the single enantiomer (levalbuterol) than when it is administered in a racemic formulation.

Hypothesis: S-albuterol increases airway hyperresponsiveness
If true, this would result in less hyperresponsiveness after administration of levalbuterol than after administration of the racemic formulation. The study by Nelson et al showed that after 4 weeks of treatment there was a small increase in baseline FEV1 with placebo or levalbuterol but not with racemic albuterol. This was statistically significant only in a subgroup of subjects using inhaled corticosteroids. The authors suggested that this might have been due to an increase in airway responsiveness caused by the S-enantiomer.

Four studies have directly tested this hypothesis using bronchoprovocation techniques .[18] [21] The brief report of Perrin-Fayolle[18] indicated a significantly lower PC20 FEV1 to methacholine 3 hours after treatment with S-albuterol in comparison with placebo. However, the other 3 studies failed to find changes in responsiveness to methacholine or adenosine monophosphate from inhalation of single[19] [20] or multiple[21] doses of S-albuterol.

Thus evidence in support of the hypothesis that S-albuterol increases airway hyperresponsiveness is at best inconclusive.

Hypothesis: S-albuterol is responsible for inducing some or all of the paradoxical bronchospasm seen with racemic albuterol
If true, this would result in a lower incidence of paradoxical bronchospasm after treatment with R-albuterol than after treatment with R,S-albuterol. Unfortunately, there are no studies that directly test this hypothetical adverse effect of S-albuterol.

Hypothesis: S-albuterol itself causes some of the systemic effects seen with inhaled albuterol
No authors of published preclinical studies or of papers that reviewed these studies have actually posed this hypothesis. Nonetheless, 2 other groups of authors have addressed this issue in normal volunteers .[22] [23] In addition, the current report by Lötvall et al[4] addresses the issue in subjects with asthma. All of these reports concluded that all observed systemic effects of racemic albuterol are due to the R-enantiomer.

So where are we now regarding a basis for decision-making? Although the preclinical data remain intriguing, available clinical data provide little support for the routine use of levalbuterol over the racemic formulation. Perhaps adverse effects of S-albuterol can be demonstrated in more severely ill asthmatic patients seen in the emergency room or intensive care unit when much larger doses are given for sustained periods. Studies in these clinical settings using appropriate methodology would be of interest.

For now, however, we have to deal with the data at hand concerning the potential benefits and costs of using pure R-albuterol over the traditional racemic formulation. Taken as a whole, the available data provide no evidence that levalbuterol is any safer or more effective than doses of racemic albuterol that contain equimolar doses of R-albuterol. Similar views have been expressed by others .[24] [25] Thus there appears to be no compelling reason to use levalbuterol rather than any other preservative-free albuterol aerosol. Considering the greater cost that is currently associated with Xopenex (Table I), routine use of this product has the potential to increase the cost of asthma care without identified benefit.

Table I. Range of costs per usual dose for different formulations of albuterol aerosol preparations taken from 4 major online-pharmacy Web sites Produce Price range per dose (US $)

Xopenex (0.63 or 1.25 mg/3 mL) 1.91 - 2.17
Albuterol (2.5 mg/3 mL) 0.80 - 0.88
Albuterol MDI(200 inhalations, 2 inhalations/dose) 0.14 - 0.20

References

1. Nelson HS, Bensch G, Pleskow WW. DiSantostefano R, DeGraw S, Reasner DS, et al. Improved bronchodilation with levalbuterol compare with racemic albuterol in patients with asthma. J Allergy Clin Immunol 1998;102:943-52. Full Text

2. Gawchik SM, Saccar CL, Noonan M, Reasner DS, DeGraw SS. The safety and efficacy of nebulized levalbuterol compared with racemic albuterol and placebo in the treatment of asthma in pediatric patients. J Allergy Clin Immunol 1999;103:615-21. Full Text

3. Handley DA, Tinkelman D, Noonan M, Rollins TE, Snider ME, Caron J. Dose-response evaluation of levalbuterol versus racemic albuterol in patients with asthma. J Asthma 2000;37:319-27. Abstract

4. Lötvall J, Palmqvist M, Arvidsson P, Maloney A, Ventresca GP, Ward J. The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients. J Allergy Clin Immunol 2001;108:726-31. Full Text

5. Mazzoni L, Naef R, Chapman ID, Morley J. Hyperresponsiveness of the airways following exposure of guinea-pigs to racemic mixtures and distomers of ß2 selective sympathomimetics. Pulm Pharmacol 1994;7:367-76. Abstract

6. Leff RA, Herrnreiter A, Naclerio RM, Baroody FM, Handley DA, Munoz NM. Effect of enantiomeric forms of albuterol on stimulated secretion of granular protein from human eosinophils. Pulm Pharmacol Ther 1997;10:97-104. Abstract

7. Handley DA, McCullough JR, Crowther SD, Morley J. Sympathomimetic enantiomers and asthma. Chirality 1998;10:262-72. Abstract

8. Waldeck B. Enantiomers of bronchodilating ß2-adrenoceptor agonists: is there a cause for concern? J Allergy Clin Immunol 1999;103:742-8. Full Text

9. Nelson HS. Clinical experience with levalbuterol. J Allergy Clin Immunol 1999;104:S77-S84. Full Text

10. Handley D. The asthma-like pharmacology and toxicology of (S)-isomers of beta agonists. J Allergy Clin Immunol 1999;104(Pt 2):S69-S76. Full Text

11. Schmekel B, Rydberg I, Norlander B, Sjöswärd KN, Ahlner J, Andersson RGG. Sterioselective pharmacokinetics of S-salbutamol after administration of the racemate in healthy volunteers. Eur Respir J 1999;13:1230-5. Abstract

12. Ahrens RC. On comparing beta adrenergic agonists. Ann Allergy 1991;67:296-8. Citation

13. Finney DJ. Statistical methods in biological assay. 3rd ed. London: Charles Griffin & Co; 1978. p. 105-47.

14. Ahrens RC, Hendeles L, Clarke WR, Dockhorn RJ, Hill MR, Vaughan LM, et al. Therapeutic equivalence of Spiros DPI and Ventolin MDI: a bioassay using methacholine. Am J Respir Crit Care Med 1999;160:1238-43. Abstract

15. Parameswaran KN, Inman MD, Ekholm BP, Morris MM, Summers E, O'Byrne PM, et al. Protection against methacholine bronchoconstriction to assess relative potency of inhaled beta2-agonist. Am J Respir Crit Care Med 1999;160:354-7. Abstract

16. Stewart BA, Ahrens RC, Carrier S, Frosolono M, Lux C, Han S-H, et al. Demonstration of in vivo bioequivalence of the Norton generic albuterol metered-dose inhaler to Ventolin. Chest 2000;117:714-21. Full Text

17. Asmus MJ, Ahrens RC, Clarke WR, Hendeles L. Therapeutic ratio of inhaled corticosteroids: fact or fiction [letter to the editor]? Am J Respir Crit Care Med. In press.

18. Perrin-Fayolle M. Salbutamol in the treatment of asthma [letter]. Lancet 1995;346:1101. Citation

19. Cockcroft DW, Swystun VA. Effect of single doses of S-salbutamol, R-salbutamol, racemic salbutamol, and placebo on the airway response to methacholine. Thorax 1997;52:845-8. Abstract

20. Ramsay CM, Cowan J, Flannery E, McLachlan C, Taylor DR. Bronchoprotective and bronchodilator effects of single doses of (S)-salbutamol, (R)-salbutamol and racemic salbutamol in patients with bronchial asthma. Eur J Clin Pharmacol 1999;55:353-9. Abstract

21. Cockcroft DW, Davis BE, Swystun VA, Marciniuk DD. Tolerance to the bronchoprotective effect of ß2 -agonists: comparison of the enantiomers of salbutamol with racemic salbutamol and placebo. J Allergy Clin Immunol 1999;103:1049-53. Full Text

22. Lipworth BJ, Clark DJ, Koch P, Arbeeny C. Pharmacokinetics and extrapulmonary beta 2 adrenoceptor activity of nebulised racemic salbutamol and its R and S isomers in healthy volunteers. Thorax 1997;52:849-52. Abstract

23. Pancu D, Evans E, LaFalmmer M, Melanson S, Stromski C, Reed J. How does the potassium-lowering effect of inhaled levalbuterol compare to that of standard albuterol? Acad Emerg Med 2001;8:496.

24. Jenne JW. The debate on S-enantiomers of ß-agonists: tempest in a teapot or gathering storm? J Allergy Clin Immunol 1998;102:893-5. Full Text

25. Asmus MJ, Hendeles L. Levalbuterol nebulizer solution: is it worth five times the cost of albuterol? Pharmacotherapy 2000;20:123-9. Abstract

COX-2 Inhibitors			
Characteristic	**Celebrex (Celecoxib).**	**Vioxx (Rofecoxib)**	**Bextra (valdecoxib)**
Pharmacology	Nonsteroidal antiinflammatory agents in clinical use inhibit both isoforms of cyclooxygenase (cyclooxygenase-1 (COX-1) and COX-2) to varying degrees. COX-1 is the constitutive isoform of the enzyme, and its inhibition appears responsible for adverse gastrointestinal and renal effects, and antiplatelet activity of this class of agents; in contrast, inhibition of the inducible COX-2 isoform is mainly responsible for antiinflammatory and analgesic properties. Selective COX-2 inhibitors are claimed to provide analgesic/antiinflammatory effects comparable to conventional nonsteroidal antiinflammatory agents, but with a reduced propensity for adverse effects.		
Generic available	No	No	No
Date of FDA Approval	December 31, 1998	May 20, 1999	November 19, 2001
Manufacturer	Pharmacia	Merck	Pharmacia
Dosage forms / route of admin	PO: 100 mg, 200 mg , 400mg Capsules	PO: 12.5 mg, 25 mg, 50 mg Tabs, 12.5 mg/5 ml and 25 mg/5 ml Susp	PO: 10 mg, 20 mg Tabs
Dosing	QD- BID	QD	QD-BID

COX-2 Inhibitors			
Characteristic	**Celebrex (Celecoxib).**	**Vioxx (Rofecoxib)**	**Bextra (valdecoxib)**
Dosing	**OA:** Recommended dosage is 200 mg/day administered as a single dose or as 100 mg twice/day. **RA:** Recommended dosage is 100 to 200 mg twice/day. **Acute pain and primary dysmenorrhea:** Recommended dose is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed. **FAP:** Continue usual medical care for FAP patients while on celecoxib. To reduce the number of adenomatous colorectal polyps in patients with FAP, the recommended oral dose is 400 mg (2 × 200 mg capsules) twice daily. Take with food. **Hepatic impairment:** The daily recommended dose of celecoxib in patients with moderate hepatic impairment (Child-Pugh Class II) should be reduced by approximately 50%.	**OA:** The recommended starting dose is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25mg. **RA:** Recommended dose is 25 mg once daily. The maximum recommended daily dose is 25 mg. **Acute pain and primary dysmenorrhea:** The recommended dose is 50 mg once daily. The maximum recommended daily dose is 50 mg. Chronic use of 50 mg/day is not recommended. Use of rofecoxib for more than 5 days in the management of pain has not been studied. **Hepatic insufficiency:** Use lowest possible dose.ed.	**OA/Adult RA:** 10 mg once daily. **Primary dysmenorrhea:** 20 mg twice daily, as needed.
Pediatric Labeling (Age)	Safety and efficacy in children under 18 years of age have not been established	Safety and efficacy in children have not been established	Safety and efficacy in children have not been established
FDA Labeled Indications	• Osteoarthritis • Adult Rheumatoid arthritis, • Acute pain • Primary Dysmenorrhea • Familial Adenomatous Polyposis	• Osteoarthritis • Adult Rheumatoid arthritis • Acute Pain • Primary Dysmenorrhea	• Osteoarthritis • Adult Rheumatoid Arthritis • Primary Dysmenorrhea

COX-2 Inhibitors			
Characteristic	**Celebrex (Celecoxib).**	**Vioxx (Rofecoxib)**	**Bextra (valdecoxib)**
Other studied uses	Under study for: ▪ Treatment of Barrett's esophagus ▪ Treatment of sporadic adenomatous polyposis / reduction of risk of colon cancer	Under study for: ▪ Treatment of colon polyps and treatment and prevention of colon cancer ▪ Chronic Pain	Under study for: ▪ Acute Pain ▪ Migraine pain
	▪ Further studies of the preventive role of COX-2 inhibitors are planned for bladder cancer and oral leukoplakia. Studies using COXIIs as adjuvants in the treatment of non-small cell lung cancer (NSCLC) with radiation +/- standard chemotherapy are ongoing.		
Contraindications	▪ In patients with known hypersensitivity to each agent ▪ Valdecoib: C/I in patients with hypersensitivity to valdecoxib or parecoxib ▪ Celecoxib, Valdecoxib: C/I in patients who have demonstrated allergic-type reactions to sulfonamides • Patients with a history of bronchospasm with rhinoconjunctivitis or urticaria/angioedema associated with aspirin or other nonsteroidal antiinflammatory agents (adult-onset asthma, chronic rhinitis, nasal polyps, and chronic urticaria/angioedema predispose to these reactions) • Patients with advanced renal disease • Patients with hepatic insufficiency • Hypertension or cardiac conditions aggravated by fluid retention and edema • Previous history of gastrointestinal ulceration, bleeding, or perforation • Medical history of of ischemic heart disease, including angina or infarction • Patients with considerable dehydration • Avoid in late pregnancy due to possible premature closure of ductus arteriosus • Concurrent celecoxib and warfarin; frequent monitoring is required upon initiation of therapy and after changes in dose		
Drug interactions	▪ Fluconazole, lithium ▪ Warfarin : Monitor patients currently on warfarin	▪ Lithium, ▪ Methotrexate ▪ Rifampin ▪ Warfarin	▪ Lithium ▪ Fluconazole & ketoconazole ▪ Warfarin: Prothrombin time should be closely monitored, especially in the first few days after initiating or changing valdecoxib therapy, in patients also receiving warfarin.

COX-2 Inhibitors			
Characteristic	**Celebrex (Celecoxib).**	**Vioxx (Rofecoxib)**	**Bextra (valdecoxib)**
Major AEs / Warnings	▪ Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine can occur at any time with or without warning symptoms. ▪ As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure. ▪ No information is available regarding the safe use in patients with advanced kidney disease. Therefore, treatment is not recommended in these patients. ▪ In late pregnancy, should be avoided because it may cause premature closure of the ductus arteriosus.		
Pharmacokinetics issues	▪ Half-life = 11hrs ▪ Mild to moderate hepatic impairment (child-pugh class I & II) patients have demonstrated a 40-180% increase in AUC, respectively	▪ Half-life = 17 hrs ▪ A study in Mild (child-pugh score<6) indicated no change in AUC relative to healthy patients while a study in moderate (child-pugh 7-9) demonstrated a 69% increase in AUC.	▪ Half-life = 8-11 hrs ▪ Valdecoxib concentrations are significantly increased (130%) in patients with moderate hepatic (child-pugh class B) impairment.
Unique Features/Advantages	▪ FAP indication	▪ Not recommended above QD dosing	▪ Recommended QD dosing

COX-2 Inhibitors			
Characteristic	**Celebrex (Celecoxib).**	**Vioxx (Rofecoxib)**	**Bextra (valdecoxib)**
Summary	• The selective COX-2 inhibitory effects of the available COXIIs are an advantage over nonselective nonsteroidal antiinflammatory agents primarily with regard to gastrointestinal toxicity; most data suggest a lower incidence of gastroduodenal ulceration. Lack of platelet effects is also an advantage in certain populations However, there is no evidence that renal events are reduced by selective COX-2 inhibitors. • In the treatment of dysmenorrhea, COX-2 inhibitors are not usually indicated unless risk factors are present. Although efficacy has been observed versus placebo in various types of postoperative pain, placebo-controlled comparisons with both nonselective and selective nonsteroidal agents are needed before it can be recommended; studies with celecoxib and rofecoxib suggest the lesser efficacy of these agents for acute pain compared to nonselective agents (ie, naproxen, ibuprofen). • Celecoxib has been shown to reduce the number of adenomatous colorectal polyps associated with familial adenomatous polyposis (FAP) over a 6-month treatment period. The use of celecoxib in FAP has not been shown to reduce the risk of gastrointestinal cancer, the need for prophylactic colectomy or other FAP-related surgeries, and the frequency of routine endoscopic surveillance should not be decreased. • Celecoxib has been compared with naproxen. The anti-inflammatory and analgesic efficacy of these agents appear similar in rheumatoid arthritis and osteoarthritis, and limited short-term studies in healthy subjects suggest improved gastrointestinal tolerability and lack of platelet effects with celecoxib. However, gastrointestinal ulceration is most prevalent during prolonged use of nonsteroidal antiinflammatory agents, and a safety advantage of celecoxib (or other similar compounds) over naproxen or other traditional agents during chronic use remains to be demonstrated. Studies using celecoxib in high-risk patients (eg, history of peptic ulcer, bleeding risk) and comparisons of the drug with other selective cyclooxygenase-2 inhibitors (eg, meloxicam, MK-966), conventional agents with some selectivity (eg, etodolac, nabumetone), and the combination of misoprostol/diclofenac (for comparative GI tolerance) are also needed. • Misoprostol/diclofenac or the separate use of misoprostol (Cytotec(R)) with other nonsteroidal agents is to be considered in patients at risk for severe gastrointestinal toxicity (eg, elderly disabled patients with a history of peptic ulcer disease or gastrointestinal bleeding). In such patients unable to tolerate misoprostol/diclofenac due to the occurrence of severe diarrhea, celecoxib or another similar agent would then be indicated. • Selective cyclooxygenase-2 (COX-2) inhibitors are known to inhibit the production of vascular prostacyclin (PGI2), an inhibitor of platelet aggregation and a vasodilator. Unlike conventional non-steroidal antiinflammatory drugs, COX-2 inhibitors do not reduce the endogenous production of thromboxane A2, a potent platelet activator and aggregator, thereby causing a potentially prothrombotic cascade of events that could lead to a significant increase in the risk for thrombotic cardiovascular events (myocardial infarction, occlusive stroke) in patients receiving celecoxib therapy. It therefore is advisable to exercise caution when prescribing celecoxib and other COX-2 inhibitors to patients with a higher risk of cardiovascular disease.		

COX-2 Inhibitors			
Characteristic	**Celebrex (Celecoxib).**	**Vioxx (Rofecoxib)**	**Bextra (valdecoxib)**
Summary (con't)	• COXIIS may be considered over nonselective agents for treatment of arthritis in patients with known risk factors for ulceration or bleeding, particularly the elderly. However, whether any one agent offers an advantage over other selective COX-2 inhibitors has not been determined. The full side-effect profile of these agents has yet to be elucidated and caution should be made before these agents are used indiscriminately.		
Pipeline Agents, future COXII or comparable agents	• Licofelone: a dual inhibitor of COX and 5-LOX enzymes inhibits production of the leukotrienes and prostaglandins, substances which are important mediators of joint destruction and that lead to inflammation and pain. The drug, currently in phase III testing, has shown similar efficacy to established NSAIDs, in addition to somewhat improved GI safety. • COX inhibiting nitric oxide donators (CINOD) Nitric oxide can stimulate gastroduodenal protection, counteract the vasoconstriction effects of NSAIDs and maintain antiplatelet effects.		

Risk of cardiovascular events associated with selective COX-2 inhibitors.
Mukherjee D, Nissen SE, Topol EJ.

JAMA. 2001 Aug 22-29;286(8):954-9.

Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, F 25, 9500 Euclid Ave, Cleveland, OH 44195, USA.

Abstract
Atherosclerosis is a process with inflammatory features and selective cyclooxygenase 2 (COX-2) inhibitors may potentially have antiatherogenic effects by virtue of inhibiting inflammation. However, by decreasing vasodilatory and antiaggregatory prostacyclin production, COX-2 antagonists may lead to increased prothrombotic activity. To define the cardiovascular effects of COX-2 inhibitors when used for arthritis and musculoskeletal pain in patients without coronary artery disease, we performed a MEDLINE search to identify all English-language articles on use of COX-2 inhibitors published between 1998 and February 2001. We also reviewed relevant submissions to the US Food and Drug Administration by pharmaceutical companies. Our search yielded 2 major randomized trials, the Vioxx Gastrointestinal Outcomes Research Study (VIGOR; 8076 patients) and the Celecoxib Long-term Arthritis Safety Study (CLASS; 8059 patients), as well as 2 smaller trials with approximately 1000 patients each. The results from VIGOR showed that the relative risk of developing a confirmed adjudicated thrombotic cardiovascular event (myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, and transient ischemic attacks) with rofecoxib treatment compared with naproxen was 2.38 (95% confidence interval, 1.39-4.00; P =002). There was no significant difference in cardiovascular event (myocardial infarction, stroke, and death) rates between celecoxib and nonsteroidal anti-inflammatory agents in CLASS. The annualized myocardial infarction rates for COX-2 inhibitors in both VIGOR and CLASS were significantly higher than that in the placebo group of a recent meta-analysis of 23 407 patients in primary prevention trials (0.52%): 0.74% with rofecoxib (P =.04 compared with the placebo group of the meta-analysis) and 0.80% with celecoxib (P =.02 compared with the placebo group of the meta-analysis). The available data raise a cautionary flag about the risk of cardiovascular events with COX-2 inhibitors. Further prospective trial evaluation may characterize and determine the magnitude of the risk.

Current perspective on the cardiovascular effects of coxibs.
Konstam MA, Weir MR.

Cleve Clin J Med. 2002;69 Suppl 1:SI47-52

Tufts University School of Medicine and the New England Medical Center, Boston, MA 02111, USA.
Abstract
Aspirin and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for their anti-inflammatory and analgesic effects. In addition, aspirin is documented to reduce cardiovascular events in selected populations, presumably because of inhibition of platelet aggregation. Yet these drugs are not without toxicity, particularly adverse effects on the gastric mucosa. The gastrointestinal toxicity of nonselective NSAIDs and aspirin derives from the inhibition of the cyclooxygenase (COX) enzyme, COX-1, which synthesizes gastroprotective prostaglandins, while the anti-inflammatory and pain-relieving effects are largely derived from inhibition of COX-2-derived prostaglandins. Available data indicate that the harmful gastric effects of nonselective NSAIDs are reduced by substitution of agents that only inhibit the COX-2 protein. The COX-2-selective inhibitors, however, have also been shown to inhibit the production of vascular prostacyclin, which has vasodilatory effects and inhibits platelet aggregation; unlike nonselective NSAIDs, they do not inhibit the production of thromboxane, an eicosanoid that promotes platelet aggregation. Whether these effects could potentially contribute to a prothrombotic environment is the subject of current, intensive debate. In the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, there was a higher incidence of cardiovascular thrombotic events in the rofecoxib- vs the naproxen-treated group: 1.67 vs 0.70 per 100 patient years. However, in a pooled analysis of rofecoxib studies, the risk of sustaining a thrombotic cardiovascular event was similar when comparing patients receiving rofecoxib with those receiving placebo, or when comparing patients receiving rofecoxib with those receiving nonnaproxen nonselective NSAIDs. These findings are likely to result, at least in part, from the antiplatelet action of naproxen, which has been shown to be potent and sustained during a typical dosing regimen (500 mg twice daily in VIGOR). In contrast, the other NSAID comparators effect weaker

and/or nonsustained antiplatelet action. In the Celecoxib Long-term Arthritis Safety Study (CLASS) trial, there was no difference between celecoxib and the nonselective NSAIDs explored (which did not include naproxen) in cardiovascular event rates. Unlike those in VIGOR, patients in the CLASS trial were allowed to take low-dose aspirin. Thus, despite concerns raised by results of VIGOR, other existing data, including those pooled from existing placebo-controlled trials, do not support a clinically relevant prothrombotic effect of the COX-2 inhibitors. Additional placebo-controlled data, from patients at both high and low risk for cardiovascular events, are warranted to clarify the cardiovascular effects of this class of agents.

An evidence-based evaluation of the gastrointestinal safety of coxibs.
B**ombardier C.** Am J Cardiol. 2002 Mar 21;89(6A):3D-9D.

Supported by an unrestricted grant from Merck and Co

Division of Clinical Decision Making and Health Care, Toronto General Research Institute, Toronto General Hospital, Toronto, Ontario, Canada.

Abstract
Nonsteroidal anti-inflammatory drugs (NSAIDs) are nonselective inhibitors of cyclooxygenase (COX) isoforms COX-1 and COX-2. NSAIDs have analgesic and anti-inflammatory properties that are proven, and they are extensively used in the treatment of arthritis, pain, and headache. Despite their good efficacy, NSAIDs are associated with significant gastrointestinal (GI) toxicity, which appears to be related to the inhibition of the cytoprotective function of COX-1. Thus, selective COX-2 inhibitors, or coxibs, were designed to inhibit only the production of COX-2-dependent inflammatory prostaglandins, without any effect on COX-1 and its gastroprotective function. This article reviews important evidence on the GI safety of coxibs. Endoscopic studies demonstrated that coxibs, such as celecoxib and rofecoxib, induced significantly fewer ulcers than nonspecific NSAIDs. To analyze whether the incidence of clinical GI events is also lower with coxibs, 2 large controlled clinical trials, the Celecoxib Long-term Arthritis Safety Study (CLASS) and Vioxx Gastrointestinal Outcomes Research (VIGOR), evaluated the GI safety of celecoxib and rofecoxib, respectively. Based on evidence from the VIGOR trial, it was demonstrated that rofecoxib has already fulfilled the promise and significantly decreases the risk of clinically important and complicated GI events compared with a nonselective NSAID, naproxen. In contrast, the CLASS trial showed that the incidence of ulcer complications in patients treated with celecoxib was similar in patients treated with nonspecific NSAIDs.

Do selective cyclo-oxygenase inhibitors eliminate the adverse events associated with nonsteroidal anti-inflammatory drug therapy?

Deviere J.
Eur J Gastroenterol Hepatol. 2002 Sep;14 Suppl 1:S29-33.

Department of Gastroenterology, University Hospital Erasme, Route de Lennik 808, Brussels 1070, Belgium.

Abstract

Among the most widely prescribed drugs worldwide, non-steroidal anti-inflammatory drugs (NSAIDs) are effective for relieving pain, but they are also associated with a high incidence of gastrointestinal (GI) adverse events. Both the beneficial and harmful effects of NSAIDs result from inhibition of the cyclo-oxygenase (COX) enzyme. Recognition of the two distinct COX isoforms prompted development of drugs that selectively block the activity of COX-2, thus providing pain relief and reducing inflammation while sparing COX-1, the enzyme apparently responsible for most protective prostaglandin synthesis in the mucosa of the stomach and duodenum. The results of preclinical and clinical studies indicate that COX-2 inhibitors exhibit high selectivity in inhibiting COX-2, provide excellent pain relief, and cause significantly less GI toxicity than do conventional nonselective NSAIDs. Although they represent a significant advance over nonselective NSAIDs, selective COX-2 inhibitors are not without limitations. They do not completely eliminate GI toxicity or the renal side effects associated with use of conventional NSAIDs. Moreover, in cases of inflammation or ulceration in the GI tract, COX-2 inhibition may delay ulcer healing. Finally, case reports and the results of animal experiments suggest that COX-2 inhibitors may adversely affect ovulation and cause a tendency towards prothrombotic events.

Gastrointestinal safety and tolerability of nonselective nonsteroidal anti-inflammatory agents and cyclooxygenase-2-selective inhibitors.

Peura DA.
Cleve Clin J Med. 2002;69 Suppl 1:SI31-9.
Division of Gastroenterology and Hepatology, University of Virginia Health System, Charlottesville 22908, USA.
DAP8V@hscmail.mcc.virginia.edu

Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all drugs and are the most common medications used by persons aged 65 years or more. NSAIDs have a number of side effects, of which the most prevalent and serious is gastrointestinal (GI) toxicity. GI side effects of NSAIDs range from dyspepsia and gastroduodenal ulcers to serious, potentially fatal GI complications including bleeding and perforation. Serious GI complications often lack warning signs; knowledge of risk factors for NSAID-related gastropathy can identify patients at high risk, allowing for initiation of the appropriate therapeutic intervention. Risk factors include advanced age, NSAID dose, prior GI complications, infection with Helicobacter pylori, and use of corticosteroids and anticoagulants. There are few well-established strategies to prevent GI complications in NSAID users. Risk assessment and cotherapy with acid suppressors (H2-receptor antagonists and proton pump inhibitors) or prostaglandin replacement (misoprostol) and H pylori eradication are beneficial. Cyclooxygenase-1 (COX-1) is a key enzyme in gastroprotective mucosal defenses, and the best way to prevent GI toxicity is to avoid drugs that inhibit COX-1. Clinical studies of the COX-2-selective inhibitors rofecoxib and celecoxib have demonstrated efficacy equivalent to nonselective NSAIDs with lower rates of GI side effects (for example, incidence of endoscopic ulcers equivalent to placebo). Selective COX-2 inhibitors (coxibs) provide effective treatment of pain and inflammation while reducing risk of gastropathy.

Hypnotics: Benzodiazepines		
Characteristic	**Restoril (temazepam)**	**Prosom (estazolam)**
Pharmacology	Appears to potentiate the effects of gamma-aminobutyrate (GABA) (i.e., facilitate inhibitory GABA neurotransmission) and other inhibitory transmitters by binding to specific benzodiazepine receptor sites. If benzodiazepines are discontinued after 3 or 4 weeks of continued use, the patient may experience REM rebound; however, REM rebound with flurazepam, quazepam and possibly estazolam is slight.	
Manufacturer	Available generically	Available generically
Generic available?	Yes (15mg, 30mg)	Yes
Dosage forms / route of admin	7.5mg, 15mg, 30mg capsules / oral	1mg, 2mg tablets / oral
General Dosing Guidelines	15 to 30 mg before bedtime	1 to 2 mg at bedtime
Pediatric Labeling	Safety and efficacy in children under age 18 has not been established.	
FDA Labeled Indications	Insomnia	
Contraindications	▪ Hypersensitivity to other benzodiazepines ▪ Pregnancy ▪ Concurrent use with ketoconazole, itraconazole and nefazodone; medications that significantly impair oxidative metabolism of triazolam mediated by cytochrome P450 3A (CYP3A)	
Drug interactions	▪ Inhibitors and Inducers of CYP450 3A3/4 ▪ Benzodiazepine effects may be increased by: CNS depressants/alcohol, cimetidine, oral contraceptives, disulfiram, isoniazid, [Temazepam may not interact; however, its half-life may be decreased by oral contraceptives.]; probenecid, macrolides. ▪ Benzodiazepine effects may be decreased by rifampin [except temazepam], smoking, theophylline. ▪ Digoxin levels and phenytoin levels may increase. ▪ Benzodiazepines may increase effects, decrease effects, or have no effects on neuromuscular blockers.	
Major AEs / Warnings	▪ Anterograde amnesia and paradoxical reactions (especially with triazolam) ▪ Signs/symptoms of depression may be intensified ▪ Sedation (daytime sleepiness more common with drugs that have long half-lives) ▪ Tolerance ▪ Dependence/Withdrawal ▪ Rebound insomnia (less likely after withdrawal of drugs with intermediate or long half-lives) ▪ Early morning insomnia (less likely with drugs that have intermediate or long half-lives) ▪ Hangover (more common with drugs that have long half-lives) ▪ Caution in patients with compromised respiratory function; respiratory depression and sleep apnea have occurred ▪ Pregnancy: Category X. ▪ Lactation: Benzodiazepines are excreted in breast milk, Therefore, administration to nursing mothers is not recommended.	
Pharmacokinetics issues	▪ Half-life 9 to 15 hours ▪ No major active metabolite	▪ Half-life 8 to 28 hours ▪ No major active metabolite

Hypnotics: Benzodiazepines		
Characteristic	**Restoril (temazepam)**	**Prosom (estazolam)**
Dosage adjustment in key populations	▪ Renal/Hepatic Impairment: Observe usual precautions under these conditions; the potential for excessive sedation or impaired coordination exists. ▪ Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines. ▪ Elderly: The risk of developing oversedation, dizziness, confusion or ataxia increases substantially with larger doses of benzodiazepines in elderly and debilitated patients. Initiate with lowest effective dose.	
Unique Features / Advantages / Efficacy / Summary	▪ Wide margin of safety between therapeutic and toxic doses. ▪ Early morning insomnia: May be more common with use of short half-life agents such as temazepam. ▪ Temazepam undergoes conjugative metabolism (which is not impaired in the elderly).	▪ Rebound Insomnia may be less likely after withdrawal of agents that have intermediate or long half-lives such as estazolam. ▪ Wide margin of safety between therapeutic and toxic doses.

Hypnotics: Benzodiazepines		
Characteristic	**Dalmane (flurazepam)**	**Doral (quazepam)**
Pharmacology	Appears to potentiate the effects of gamma-aminobutyrate (GABA) (i.e., facilitate inhibitory GABA neurotransmission) and other inhibitory transmitters by binding to specific benzodiazepine receptor sites. If benzodiazepines are discontinued after 3 or 4 weeks of continued use, the patient may experience REM rebound; however, REM rebound with flurazepam, quazepam and possibly estazolam is slight.	
Manufacturer	Generically available	Wallace
Date of FDA Approval	N/a	December 27, 1985
Generic Available?	Yes	No
Dosage forms / route of admin	15mg, 30mg capsules / oral	7.5mg, 15mg tablets / oral
General Dosing Guidelines	30 mg before bedtime, 15 mg may be adequate for some	Initiate at 15 mg, may reduce to 7.5 mg for some
Pediatric Labeling	Safety and efficacy in children under age 18 has not been established.	Safety and efficacy in children has not been established
FDA Labeled Indications	Insomnia	
Contraindications	▪ Hypersensitivity to other benzodiazepines ▪ Pregnancy ▪ Established or suspected sleep apnea (quazepam) ▪ Concurrent use with ketoconazole, itraconazole and nefazodone; medications that significantly impair oxidative metabolism of triazolam mediated by cytochrome P450 3A (CYP3A)	
Drug interactions	▪ Inhibitors and Inducers of CYP450 3A3/4 ▪ Benzodiazepine effects may be increased by: CNS depressants/alcohol, cimetidine, oral contraceptives, disulfiram, isoniazid, [Temazepam may not interact; however, its half-life may be decreased by oral contraceptives.]; probenecid, macrolides. ▪ Benzodiazepine effects may be decreased by rifampin [except temazepam], smoking, theophylline. ▪ Digoxin levels and phenytoin levels may increase. ▪ Benzodiazepines may increase effects, decrease effects, or have no effects on neuromuscular blockers.	
Major AEs / Warnings	▪ Anterograde amnesia and paradoxical reactions (especially with triazolam) ▪ Signs/symptoms of depression may be intensified ▪ Sedation (daytime sleepiness more common with drugs that have long half-lives) ▪ Tolerance ▪ Dependence/Withdrawal ▪ Rebound insomnia (less likely after withdrawal of drugs with intermediate or long half-lives) ▪ Early morning insomnia (less likely with drugs that have intermediate or long half-lives) ▪ Hangover (more common with drugs that have long half-lives) ▪ Caution in patients with compromised respiratory function; respiratory depression and sleep apnea have occurred ▪ Pregnancy: Category X. ▪ Lactation: Benzodiazepines are excreted in breast milk, Therefore, administration to nursing mothers is not recommended.	

Hypnotics: Benzodiazepines		
Characteristic	**Dalmane (flurazepam)**	**Doral (quazepam)**
Pharmacokinetics issues	▪ Half-life of parent drug 2 to 3 hours ▪ Half-life of major active metabolite 40 to 114 hours	▪ Half-life of parent drug 25 to 41 hours ▪ Half-life of major active metabolite 28 to 114 hours
Dosage adjustment in key populations	▪ Renal/Hepatic Impairment: Observe usual precautions under these conditions; the potential for excessive sedation or impaired coordination exists. ▪ Observe usual precautions under these conditions; the potential for excessive sedation or impaired coordination exists. ▪ Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines. ▪ Elderly: The risk of developing oversedation, dizziness, confusion or ataxia increases substantially with larger doses of benzodiazepines in elderly and debilitated patients. Initiate with lowest effective dose.	
Unique Features / Advantages / Efficacy / Summary	▪ Most of the activity of flurazepam is in its desalkylflurazepam metabolite, which takes about 24 hours to accumulate; as a result, it may not be as effective as other benzodiazepines on the first night. ▪ Rebound Insomnia may be less likely after withdrawal of agents that have intermediate or long half-lives such as flurazepam ▪ Wide margin of safety between therapeutic and toxic doses.	▪ Wide margin of safety between therapeutic and toxic doses. ▪ Rebound Insomnia may be less likely after withdrawal of agents that have intermediate or long half-lives such as quazeapam.

Hypnotics: Benzodiazepines	
Characteristic	**Halcion (triazolam)**
Pharmacology	Appears to potentiate effects of gamma-aminobutyrate (GABA) (i.e., facilitate inhibitory GABA neurotransmission) and other inhibitory transmitters by binding to specific benzodiazepine receptor sites. If benzodiazepines are discontinued after 3 or 4 weeks of continued use, the patient may experience REM rebound; however, REM rebound with flurazepam, quazepam and possibly estazolam is slight.
Generic available?	Yes
Dosage forms / route of admin	0.125mg, 0.25mg tablets / oral
General Dosing Guidelines	0.125 to 0.5 mg before bedtime.
Pediatric Labeling	Safety and efficacy in children has not been established.
FDA Labeled Indications	Insomnia
Contraindications	▪ Hypersensitivity to other benzodiazepines ▪ Pregnancy ▪ Concurrent use with ketoconazole, itraconazole and nefazodone; medications that significantly impair oxidative metabolism of triazolam mediated by cytochrome P450 3A (CYP3A)
Drug interactions	▪ Inhibitors and Inducers of CYP450 3A3/4 ▪ Benzodiazepine effects may be increased by: CNS depressants/alcohol, cimetidine, oral contraceptives, disulfiram, isoniazid, [Temazepam may not interact; however, its half-life may be decreased by oral contraceptives.]; probenecid, macrolides. ▪ Benzodiazepine effects may be decreased by rifampin [except temazepam], smoking, theophylline. ▪ Digoxin levels and phenytoin levels may increase. ▪ Benzodiazepines may increase effects, decrease effects, or have no effects on neuromuscular blockers.
Major AEs / Warnings	▪ Anterograde amnesia and paradoxical reactions (especially with triazolam) ▪ Signs/symptoms of depression may be intensified ▪ Sedation (daytime sleepiness more common with drugs that have long half-lives) ▪ Tolerance ▪ Dependence/Withdrawal ▪ Rebound insomnia (less likely after withdrawal of drugs with intermediate or long half-lives) ▪ Early morning insomnia (less likely with drugs that have intermediate or long half-lives) ▪ Hangover (more common with drugs that have long half-lives) ▪ Caution in patients with compromised respiratory function; respiratory depression and sleep apnea have occurred ▪ Pregnancy: Category X. ▪ Lactation: Benzodiazepines are excreted in breast milk, Therefore, administration to nursing mothers is not recommended.
Pharmacokinetics issues	▪ Half life 1.5 to 5.5 hours ▪ No major active metabolite

Hypnotics: Benzodiazepines	
Characteristic	**Halcion (triazolam)**
Dosage adjustment in key populations	▪ Renal/Hepatic Impairment: Observe usual precautions under these conditions; the potential for excessive sedation or impaired coordination exists. ▪ Observe usual precautions under these conditions; the potential for excessive sedation or impaired coordination exists. ▪ Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines. ▪ Elderly: The risk of developing oversedation, dizziness, confusion or ataxia increases substantially with larger doses of benzodiazepines in elderly and debilitated patients. Initiate with lowest effective dose.
Unique Features / Advantages / Efficacy / Summary	▪ Wide margin of safety between therapeutic and toxic doses. ▪ Benzodiazepines with short half-lives should be discontinued gradually rather than abruptly to minimize discontinuation syndromes (recurrence, rebound, and withdrawal) ▪ Early morning insomnia: May be more common with use of short half-life agents such as triazolam

Hypnotics: Non-benzodiazepine GABA-Receptor Modulators		
Characteristic	**Ambien (zolpidem)**	**Sonata (zaleplon)**
Pharmacology	Subunit modulation of the GABA receptor chloride channel macromolecular complex is hypothesized for its sedative drug properties. In contrast to the benzodiazepines, zolpidem and zaleplon combine selectively with the omega-1 receptor of the GABA-BZ receptor complex, which may explain their relative lack of muscle relaxant and anticonvulsant actions, and their preservation of stage 3-4 deep sleep in humans.	
Manufacturer	Sanofi	Elan
Date of FDA Approval	December 16, 1992	August 13, 1999
Generic available?	No	No
Dosage forms / route of admin	5, 10mg tablet / oral	5, 10mg capsule / oral
General Dosing Guidelines	10 mg immediately before bedtime. Total dose should not exceed 10 mg.	10 mg; 5 mg may be adequate, 20 mg occasionally for those not responding to 10 mg. Dose is taken immediately before bedtime. Doses above 20mg are not recommended.
Pediatric Labeling	Safety and efficacy in children under age 18 has not been established.	Safety and efficacy in children has not been established.
FDA Labeled Indications	Insomnia	Insomnia
Contraindications	hypersensitivity to zolpidem products	hypersensitivity to zaleplon products; severe liver impairment
Drug interactions	Ethanol, Imipramine, Chlorpromazine, Potent CYP3A4 Inducers (rifampin), Sertraline, Ketoconazole, Ritonavir.	Ethanol, Imipramine, Thioridazine, Cimetidine, Potent CYP3A4 Inducers (rifampin).
Major AEs / Warnings	▪ Most common; >placebo: Drowsiness, dizziness, headache, diarrhea, drugged feeling. ▪ Pregnancy: Category B. ▪ Lactation: Between 0.004% and 0.019% of the total administered dose is excreted into breast milk, but the effect of zolpidem on the infant is unknown. The use of zolpidem in nursing mothers is not recommended.	▪ = 5%; >placebo: Abdominal pain, asthenia, headache, dyspepsia, nausea, myalgia, dizziness, somnolence. ▪ Pregnancy: Category C. ▪ Lactation: A small amount of zaleplon is excreted in breast milk with the highest excreted amount occurring during a feeding at ≈1 hour after administration. Because the effects of zaleplon on a nursing infant are not known, the use of zaleplon in nursing mothers is not recommended.
Pharmacokinetics issues	▪ Half-life 1.4 to 3.8 hours ▪ Converted to inactive metabolites that are eliminated primarily by renal excretion. ▪ Pharmacokinetics were not significantly different in renally impaired patients; therefore, no dosage adjustment is necessary. ▪ Food decreases the AUC and Cmax.	▪ Half-life of about 1 hour ▪ Well absorbed, its absolute bioavailability is approx. 30% because it undergoes significant presystemic metabolism ▪ Primarily metabolized by aldehyde oxidase and to a lesser extent by CYP3A4 ▪ A high-fat/heavy meal prolongs the absorption.

Hypnotics: Non-benzodiazepine GABA-Receptor Modulators		
Characteristic	**Ambien (zolpidem)**	**Sonata (zaleplon)**
Dosage adjustment in key populations	▪ Hepatic insufficiency: an initial 5mg dose is recommended ▪ Elderly and debilitated patients may be more sensitive to the effects of hypnotics; therefore, the recommended dose for these patients is 5mg.	▪ Treat patients with mild-to-moderate hepatic impairment with 5mg because of reduced clearance. Do not use in patients with severe hepatic impairment. ▪ Elderly and debilitated patients appear to be more sensitive to the effects of hypnotics; therefore, the recommended dose for these patients is 5mg. Doses > 10mg are not recommended.
Unique Features / Advantages / Efficacy / Summary	▪ Product information for zolpidem states memory problems can be avoided if zolpidem is taken when patients are able to get a full night's sleep (7-8 hours) before activity	▪ Product information for zaleplon states that memory problems can be avoided if zaleplon is taken only when patients are able to get 4 or more hours of sleep before activity.

New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon.

Terzano MG, Rossi M, Palomba V, Smerieri A, Parrino L.

Drug Saf. 2003;26(4):261-82
Sleep Disorders Center, University of Parma, Parma, Italy. mterzano@unipr.it

Abstract

Insomnia affects 30-35% of people living in developed countries. The impact of insomnia on daytime functioning and its relationship with medical and psychiatric illnesses necessitate early treatment to prevent insomnia becoming persistent and to avoid the development of complications. However, pharmacological strategies must achieve a balance between sedative and adverse effects. In the last 30 years, benzodiazepines have been the preferred drugs for the treatment of insomnia. Benzodiazepines act nonselectively at two central receptor sites, named omega(1) and omega(2), which are located in different areas of the CNS. The sedative action of benzodiazepines is related to omega(1) receptors, whereas omega(2) receptors are responsible for their effects on memory and cognitive functioning. According to their pharmacokinetic profile, benzodiazepines can be classified into three groups: short half-life (<3 hours), medium half-life (8-24 hours) and long half-life (>24 hours). The newer non-benzodiazepine agents zopiclone, zolpidem and zaleplon have a hypnosedative action comparable with that of benzodiazepines, but they display specific pharmacokinetic and pharmacodynamic properties. These three 'Z' agents all share a short plasma half-life and limited duration of action. In addition, these agents are selective compounds that interact preferentially with omega(1) receptors (sedative effect), whereas benzodiazepines also interact with omega(2) receptors (adverse effects on cognitive performance and memory). Zaleplon is characterised by an ultrashort half-life (approximately 1 hour). Zolpidem and zopiclone have longer half-lives (approximately 2.4 and 5 hours, respectively). These properties, together with the low risk of residual effect, may explain the limited negative influences of these agents on daytime performance. Psychomotor tasks and memory capacities appear to be better preserved by non-benzodiazepine agents than by benzodiazepines. When present, cognitive deficits almost exclusively coincide with the peak plasma concentration. In particular, impairment can emerge in the first hours after drug administration, whereas psychomotor and memory tests carried out 7-8 hours later (i.e. in the morning) generally show no relevant alterations. As with benzodiazepines, the three 'Z' non-benzodiazepine agents should be used for a limited period, even in chronic relapsing conditions. Further evaluation is needed of the safety of hypnosedative medications in the long-term management of insomnia.

Comparison of the effects of zaleplon, zolpidem, and triazolam on memory, learning, and psychomotor performance.

Troy SM, Lucki I, Unruh MA, Cevallos WH, Leister CA, Martin PT, Furlan PM, Mangano R.
J Clin Psychopharmacol. 2000 Jun;20(3):328-37

Wyeth-Ayerst Research, Radnor, Pennsylvania 19087, USA. troys@war.wyeth.com

Abstract
Twenty-four healthy male and female subjects, who participated in this randomized, double-blind, crossover study, received single nighttime doses of zaleplon 10 mg (therapeutic dose), zaleplon 20 mg, zolpidem 10 mg (therapeutic dose), zolpidem 20 mg, triazolam 0.25 mg (positive control), and placebo. Subjective behavioral ratings and psychomotor tests were completed before and 1.25 and 8.25 hours after administration of the study drug. The Immediate and Delayed Word Recall tests and the Digit Span Test were used to assess memory. The Digit-Symbol Substitution Test, Paired Associates Learning Test, and Divided Attention Test were used to assess other cognitive skills. Zaleplon 10 mg did not produce any significant changes in memory or learning compared with placebo. All other active treatments, including zolpidem 10 mg, caused psychomotor impairment at the 1.25-hour test battery. Zolpidem 20 mg (twice the therapeutic dose) produced more psychomotor impairment at the 1.25-hour assessment than did any of the other active treatments, including zaleplon 20 mg. At the 8.25-hour time point, test scores for subjects who received zaleplon 10 mg and 20 mg did not differ from the test scores for those who received placebo. However, cognitive impairment persisted up to the 8.25-hour observation for subjects who were administered triazolam 0.25 mg and zolpidem 20 mg. Adverse events associated with the use of zaleplon were transient and mild-to-moderate in severity. Overall, this study shows that zaleplon is a safe hypnotic that does not affect memory, learning, or psychomotor skills associated with vigilance.

Beyond benzodiazepines: alternative pharmacologic agents for the treatment of insomnia.

Wagner J, Wagner ML, Hening WA.
Ann Pharmacother. 1998 Jun;32(6):680-91.

College of Pharmacy, Rutgers State University of New Jersey, Piscataway 08854, USA.

Abstract

OBJECTIVE: To review the epidemiology, etiology, and classification of insomnia and provide an overview of the pharmacologic therapy of insomnia. Novel nonbenzodiazepine hypnotics including zolpidem, zopiclone, and zaleplon, as well as nonprescription products such as valerian and melatonin, are reviewed in detail. DATA SOURCES: A MEDLINE search was performed to identify relevant clinical studies, case reports, abstracts, and review articles published between April 1992 and December 1997. Key search terms included insomnia, benzodiazepines, zolpidem, zopiclone, zaleplon, Cl 284,846, melatonin, and valerian. Additional references were obtained from the lists of review articles and textbooks. DATA EXTRACTION AND SYNTHESIS: Data concerning the safety and efficacy of the hypnotic agents were extracted from all available clinical trials and abstracts. Background information regarding insomnia, benzodiazepines, and other hypnotics was extracted from the most current literature, including review articles and textbooks. CONCLUSIONS: New developments in benzodiazepine receptor pharmacology have introduced novel nonbenzodiazepine hypnotics that provide comparable efficacy to benzodiazepines. **Although they may possess theoretical advantages over benzodiazepines based on their unique pharmacologic profiles, they offer few, if any, significant advantages in terms of adverse effects.** Over-the-counter agents such as valerian and melatonin may be useful in alleviating mild, short-term insomnia, but further clinical trials are required to fully evaluate their safety and efficacy.

Tolerability of hypnosedatives in older patients.
Wortelboer U, Cohrs S, Rodenbeck A, Ruther E.

Drugs Aging. 2002;19(7):529-39.

Department of Psychiatry and Psychotherapy, Sleep Research Center, Georg-August-University of Gottingen, von-Siebold-Strasse 5, 37075 Gottingen, Germany. uwortel@gwdg.de

Abstract
Sleep disturbances are common and prevalence rates increase with age. Especially in the elderly, somatic diseases and medications with adverse effects relating to sleep are frequent reasons for disturbed and nonrefreshing sleep. It should be emphasised that these reasons must be excluded before symptomatic therapy is started. In some cases the use of hypnosedatives may be included as part of the treatment of a somatic disease and may cause sleep disturbances. Pharmacotherapy is one of the main approaches in the management of primary insomnia and should be part of a broader treatment strategy including nonpharmacological methods. This article focuses on the tolerability of frequently prescribed hypnosedatives in the elderly with primary insomnia and addresses the primary care physician. In general, recommendations for the pharmacotherapy of insomnia in elderly patients include using a reduced dosage. For some substances (e.g. zolpidem, zopiclone, zaleplon, temazepam and triazolam) the recommended dosage is half that recommended for younger patients. The properties of the selected hypnosedative should be taken into consideration and matched with the type of sleep disturbance experienced by the patient. Ultrashort-acting drugs may be useful when initiating sleep is the main problem, whereas short- and intermediate-acting substances are recommended for maintaining sleep. Possible interactions with pre-existing medication must also be taken into consideration. Some agents such as antipsychotics, antidepressants, melatonin and herbal agents may be used in specific indications. However, only a few of these substances have proven tolerability in the elderly and further investigations are recommended.

Safety of zaleplon in the treatment of insomnia.

Israel AG, Kramer JA.
Ann Pharmacother. 2002 May;36(5):852-9.

Department of Internal Medicine, School of Medicine, University of California San Diego, 4060 4th Avenue, Suite 505, San Diego, CA 92103-2121, USA. aisrael@pol.net

Abstract

OBJECTIVE: To evaluate the safety of zaleplon, a quick-acting, rapidly eliminated nonbenzodiazepine (non-BZD) hypnotic, as described in clinical investigations of adult and/or elderly subjects. DATA SOURCES: Published and presented studies evaluating zaleplon, a novel non-BZD, were identified via MEDLINE (1995-July 2001), Current Contents (ISI database), bibliographic reviews, and consultation with sleep specialists who also identified published abstracts containing data not yet published in peer-reviewed journals. DATA SYNTHESIS: Transient and chronic insomnia are common problems that should be clinically evaluated and appropriately treated. BZDs have been a primary pharmacotherapy for treating insomnia, despite their disadvantages. Newer hypnotics, characterized by increased receptor-binding specificity and favorable pharmacokinetics, provide potentially better alternatives to BZDs. Assessments included residual sedation, psychomotor impairment, or cognitive dysfunction during treatment, as well as the occurrence of rebound insomnia and withdrawal effects after discontinuation of therapy. CONCLUSIONS: Zolpidem, the first non-BZD hypnotic, appears to have short- and long-term safety profiles similar to those of the BZD triazolam. Zaleplon, a newer non-BZD sleep medication, has a quick onset of action and undergoes rapid elimination, which results in a better safety profile than previously available agents. Additionally, rebound insomnia and other withdrawal effects have not been demonstrated with zaleplon, and the drug is well tolerated in both young and elderly patients. These characteristics may be clinically advantageous for patients who should not receive BZDs.

Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia.

Smith MT, Perlis ML, Park A, Smith MS, Pennington J, Giles DE, Buysse DJ.
Am J Psychiatry. 2002 Jan;159(1):5-11.

Department of Psychiatry, Johns Hopkins University, Baltimore, MD 21287-7218, USA.
msmith62@jhmi.edu

Abstract

OBJECTIVE: Although four meta-analytic reviews support the efficacy of pharmacotherapy and behavior therapy for the treatment of insomnia, no meta-analysis has evaluated whether these treatment modalities yield comparable outcomes during acute treatment. The authors conducted a quantitative review of the literature on the outcome of the two treatments to compare the short-term efficacy of pharmacotherapy and behavioral therapy in primary insomnia. METHOD: They identified studies from 1966 through 2000 using MEDLINE, psycINFO, and bibliographies. Investigations were limited to studies using prospective measures and within-subject designs to assess the efficacy of benzodiazepines or benzodiazepine receptor agonists or behavioral treatments for primary insomnia. Benzodiazepine receptor agonists included zolpidem, zopiclone, and zaleplon. Behavioral treatments included stimulus control and sleep restriction therapies. Twenty-one studies summarizing outcomes for 470 subjects met inclusion criteria. RESULTS: Weighted effect sizes for subjective measures of sleep latency, number of awakenings, wake time after sleep onset, total sleep time, and sleep quality before and after treatment were moderate to large. There were no differences in magnitude between pharmacological and behavioral treatments in any measures except latency to sleep onset. Behavior therapy resulted in a greater reduction in sleep latency than pharmacotherapy. CONCLUSIONS: Overall, behavior therapy and pharmacotherapy produce similar short-term treatment outcomes in primary insomnia.

Management of insomnia.

Kirkwood CK.
J Am Pharm Assoc (Wash). 1999 Sep-Oct;39(5):688-96.

School of Pharmacy, Virginia Commonwealth University, Richmond 23298-0533, USA.
cynthia.kirkwood@vcu.edu

Abstract
OBJECTIVE: To review current issues in the pharmacologic and nonpharmacologic management of insomnia. DATA SOURCES: Controlled trials and case studies identified via MEDLINE for 1990 through April 1999 under the search terms insomnia, hypnotics, flurazepam, quazepam, estazolam, temazepam, triazolam, zolpidem, zaleplon, L-846, CL-284,846, melatonin, and valerian. DATA SYNTHESIS: Insomnia is a common, undertreated disorder. Nonpharmacologic management strategies (e.g., stimulus control, relaxation therapy, sleep hygiene) are therapeutic options that, compared with medication use, provide more sustained effects. The benzodiazepines and zolpidem are the most commonly prescribed hypnotic agents, but their use is associated with tolerance and central nervous system adverse effects. A new nonbenzodiazepine hypnotic agent, zaleplon, was very recently approved in the United States. Because of its short half-life, zaleplon will be useful in patients experiencing difficulty in falling asleep and in those who wake up at night and have trouble falling back to sleep. Antidepressants, antihistamines, and alternative medications are other treatment options. To avoid complications of therapy, hypnotic agents should be used at their lowest possible doses and for limited treatment durations. CONCLUSION: Pharmacotherapy is currently the most common treatment modality for insomnia, but long-term use of hypnotic agents can become complicated by drug tolerance, dependence, or rebound insomnia. Nonpharmacologic options--including combinations of behavioral interventions, sleep-restriction therapy, and patient education--provide longer-lasting benefits.

HMG-CoA Reductase Inhibitors			
Characteristic	**Lipitor (Atorvastatin)**	**Lescol, Lescol XL (Fluvastatin and Fluvastatin Extended Release)**	**Mevacor (Lovastatin) Altocor (Extended Release Lovastatin)**
Pharmacology	These agents, also referred to as the statins, competitively inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-coA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. This conversion is an early rate-limiting step in cholesterol biosynthesis. HMG-CoA reductase inhibitors increase HDL cholesterol and decrease LDL-C, total-C, apolipoprotein B, VLDL cholesterol, and plasma trigycerides.		
Manufacturer	Parke-Davis	Novartis	Merck (Mevacor) Andrx (Altocor)
Date of Approval	12/17/96	12/31/93	8/13/87 (Mevacor) 6/26/02 (Altocor)
Generic available?	No	No	Yes for Mevacor No for Altocor
Dosage forms / route of admin.	Tablets: 10, 20, 40, 80 mg	Lescol Capsules: 20, 40 mg Lescol XL Tablets, extended-release: 80 mg	Tablets: 10, 20, 40 mg Exrtended Release Tablets: 10, 20, 40, 60mg
General Dosing Guidelines	Dosage range is 10-80mg QD at any time of the day with or without food	**IR:** Dosage range is 20-80mg (given QD or BID) Lescol: Starting dose for LDL reduction of 25% or more is 40mg as one capsule, 80mg as one tablet given in the evening, or 80mg in divided doses of the 40mg capsule given twice daily. For those requiring less than 25% reduction of LDL 20mg QD may be used **Lescol XL**: 80mg QD	**IR**: Recommended dosage range is 10mg-80mg in a single or twice divided daily dose. **Extended Release:** 10 to 60 mg /day in a single dose
Pediatric Labeling	• Pediatric patients 10 to 17 yoa: starting dose of 10mg/day to a recommended maximum of 20 mg/day.	▪ Not FDA indicated for children	▪ Adolescents 10 to 17 yoa with heterozygous familial hypercholesterolemia (immediate release only)
FDA Labeled Indications	▪ Primary hypercholesterolemia and mixed dyslipidemia (IIa, IIb) ▪ Hypertriglyceridemia (IV) ▪ Primary dysbetalipoproteinemia (III) ▪ Familial hypercholesterolemia	▪ Primary hypercholesterolemia and mixed dyslipidemia (IIa, IIb) ▪ Slow progression of coronary atherosclerosis	▪ Primary hypercholesterolemia and mixed dyslipidemia (IIa, IIb)- not indicated to ↓ Apo B, ↓ TG, ↑ HDL, but produces changes similar to other agents ▪ ↓ risk of coronary heart disease in patients with average to moderately elevated total-C and LDL-C and below average HDL-C levels ▪ Slow progression of coronary atherosclerosis
Other Studied Uses	• Cognitive impairment/Dementia • Alzheimers Disease • Osteoporosis		

HMG-CoA Reductase Inhibitors			
Characteristic	**Lipitor (Atorvastatin)**	**Lescol, Lescol XL (Fluvastatin and Fluvastatin Extended Release)**	**Mevacor (Lovastatin) Altocor (Extended Release Lovastatin)**
Contraindications	Hypersensitivity to any component of these products; active liver disease or unexplained persistent elevated liver function tests; pregnancy, lactation.		
Drug interactions	▪ Antacids, Antipyrine, colestipol, cimetidine, digoxin, erythromycin, niacin, oral contraceptives, phenytoin, warfarin	▪ Diazepam, phenytoin, warfarin, amitriptyline, diclofenac, glipizide, ibuprofen, imipramine, indomethacin, and omeprazole	▪ Alcohol, azole antifungals (itraconazole, ketoconazole), cyclosporin, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, fibric acid derivatives, niacin
Major AEs / Warnings	Major AEs (not all inclusive) ▪ These agents are generally well tolerated; adverse reactions are usually mild and transient. ▪ Nausea, fatigue, headache, skin rash, myalgia, and change in bowel function. ▪ Less common, but clinically more important side effects include proximal myopathy and elevations in liver enzymes. Warnings (not all inclusive) ▪ Pregnancy Category X, Skeletal muscle effects, Endocrine effects, Hepatic function impairment, Renal function impairment, Carcinogenesis		
Dosage adjustment in key populations	Plasma levels not affected by renal disease;markedly increased with chronic alcoholic liver disease. Atorvastatin is subject to first-pass hepatic metabolism. Hepatic blood flow and hepatic size decrease with age in humans. Plasma atorvastatin concentrations depend on hepatic clearance, which is influenced by hepatic blood flow, liver size, bile flow, and intrinsic clearance. Thus, the age-related changes in pharmacokinetic parameters observed with atorvastatin may be related to these hepatic changes	Plasma concentrations are not affected by age	Renal function impairment: Ccr < 30 mL/min carefully consider dosage increases > 20 mg/day and, if deemed necessary, implement cautiously. No dosage adjustment is needed in geriatric patients.

HMG-CoA Reductase Inhibitors			
Characteristic	**Crestor (rosuvastatin) (not marketed currently)**	**Pravachol (Pravastatin)**	**Zocor (Simvastatin)**
Pharmacology	The potency of rosuvastatin for inhibiting HMG-CoA reductase was usually greater than that of other statins (ie, atorvastatin, simvastatin, pravastatin, lovastatin, cerivastatin, fluvastatin) in preclinical studies (rat and human liver microsomes; purified preparation of the catalytic domain of the human enzyme) In studies with the purified human catalytic domain, the 50% inhibitory concentration for rosuvastatin was 5.4 nanomoles (nM), compared to 8.2, 11.2, and 44.1 nM for atorvastatin, simvastatin, and pravastatin, respectively. The potency of rosuvastatin as an inhibitor of cholesterol synthesis was greater than that of atorvastatin, simvastatin, cerivastatin, fluvastatin, and pravastatin in rat hepatocytes.	These agents, also referred to as the statins, competitively inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-coA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. This conversion is an early rate-limiting step in cholesterol biosynthesis. HMG-CoA reductase inhibitors increase HDL cholesterol and decrease LDL-C, total-C, apolipoprotein B, VLDL cholesterol, and plasma trigycerides.	
Manufacturer	AstraZeneca	Bristol- Myers Squibb	Merck
Date of Approval	Recommended by Advisory Panel to the FDA , but not yet FDA approved	10/31/91	12/23/91
Generic available?	No	No	No
Dosage forms / route of admin.	Proposed: 5mg (for patients receiving CYA) 10, 20and 40mg	Tablets: 10, 20, 40, 80mg	Tablets: 5, 10, 20, 40, 80 mg
General Dosing Guidelines	Expected: 10-40mg once daily; max 40mg/day	QD	▪ QD ▪ Homozygous familial hypercholesterolemia: TID
Pediatric Labeling	N/a	▪ Children 8 to 13 yoa: 20mg/day; doses greater than 20mg have not been studied ▪ Adolescents 14 to 18 yoa: 40mg/day; doses greater than 40mg have not been studied	▪ Not FDA indicated for children

HMG-CoA Reductase Inhibitors			
Characteristic	**Crestor (rosuvastatin) (not marketed currently)**	**Pravachol (Pravastatin)**	**Zocor (Simvastatin)**
FDA Labeled Indications	Proposed indications: • Primary hypercholesterolemia and mixed dyslipidemia • Hypertriglyceridemia • Homozygous familial hypercholesterolemia	▪ Primary hypercholesterolemia and mixed dyslipidemia (IIa, IIb) ▪ Hypertriglyceridemia (IV) ▪ Primary dysbetalipoproteinemia (III) Primary Prevention ▪ ↓ risk of myocardial infarction ▪ ↓ risk of undergoing a revascularization procedure ▪ ↓ risk of cardiovascular mortality with no increase in death from non-cardiovascular causes Secondary Prevention ▪ ↓ risk of total mortality by decreasing coronary death ▪ ↓ risk of myocardial infarction ▪ ↓ risk of undergoing a revascularization procedure ▪ ↓ risk of stroke and TIA ▪ Slow progression of coronary atherosclerosis	▪ Primary hypercholesterolemia and mixed dyslipidemia (IIa, IIb) ▪ Hypertriglyceridemia (IV) ▪ Primary dysbetalipoproteinemia (III) ▪ Familial hyperlipidemia Secondary Prevention ▪ ↓ risk of total mortality by decreasing coronary death ▪ ↓ risk of myocardial infarction ▪ ↓ risk of undergoing a revascularization procedure ▪ ↓ risk of stroke and TIA
Other studied uses	• Cognitive impairment/Dementia • Alzheimers Disease • Osteoporosis		
Contraindications	• Prior hypersensitivity to rosuvastatin • Pregnancy or breastfeeding period (based on data for other statins) • Liver disease (potential for exacerbation) Conditions associated with/predisposing to renal failure secondary to rhabdomyolysis (eg, severe infection, hypotension, metabolic or electrolyte disorders, trauma, major surgery, uncontrolled seizures) (risk of renal failure if rhabdomyolysis occurs)	Hypersensitivity to any component of these products; active liver disease or unexplained persistent elevated liver function tests; pregnancy, lactation.	
Drug interactions	Expected: • Cyclosporine	No significant drug interactions with CYP3A4 or CYP2C9	Alcohol, azole antifungals (itraconazole, ketoconazole), cyclosporin, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, fibric acid derivatives, niacin

HMG-CoA Reductase Inhibitors			
Characteristic	**Crestor (rosuvastatin) (not marketed currently)**	**Pravachol (Pravastatin)**	**Zocor (Simvastatin)**
Major AEs / Warnings	Proposed: • Myopathy • Myalgias • Respiratory Tract Infections • Headache • GI distress	Major AEs (not all inclusive) ▪ These agents are generally well tolerated; adverse reactions are usually mild and transient. ▪ Nausea, fatigue, headache, skin rash, myalgia, and change in bowel function. ▪ Less common, but clinically more important side effects include proximal myopathy and elevations in liver enzymes. Warnings (not all inclusive) ▪ Pregnancy Category X, Skeletal muscle effects, Endocrine effects, Hepatic function impairment, Renal function impairment, Carcinogenesis	
Dosage adjustment in key populations	Approximately 10% of an oral dose is excreted in the urine, primarily as unchanged drug. Based on data for other statins, this may result in plasma accumulation and potential adverse effects (eg, myopathy). Dose reductions are suggested in renal impairment, although specific guidelines are unavailable.	Renal/Hepatic function impairment: Use a starting dose of 10 mg/day in significant renal or hepatic function impairment.	Exercise caution when simvastatin is administered to patients with severe renal insufficiency. Initiate therapy in such patients with 5 mg/day and monitor closely.
Note:	Endocrinologic and Metabolic Advisory Committee to the U.S. Food and Drug Administration (FDA) voted unanimously to recommend approval for CRESTOR® (rosuvastatin calcium) The 80mg dose was suspended due to safety concerns in 3/2002 May 2002: FDA requested further data on the 20 and 40 mg dose for 24 weeks and additional information on renal effects		
Pipeline Agents	Pitavastatin		

HMG-COA Reductase Inhibitor Combinations	
Characteristic	**Advicor (lovastatin plus niacin extended release)**
Pharmacology	**Niacin Extended Release**: Nicotinic acid (but not nicotinamide) in gram doses produces an average 10% to 20% reduction in total and LDL cholesterol, a 30%to 70% reduction in triglycerides, and an average 20% to 35% increase in HDL cholesterol. Nicotinic acid also decreases serum levels of apolipoprotein B-100, the major component of VLDL and LDL fractions. The mechanism by which nicotinic acid exerts these effects is not entirely understood but may involve several actions, including a decrease in esterification of hepatic triglycerides. The effect of nicotinic acid-induced changes in lipids/lipoproteins on cardiovascular morbidity and mortality in individuals without pre-existing coronary disease has not been established. **Lovastatin**: See HMG-COA Reductase Inhibitors
Manufacturer	KOS
Date of Approval	DEC 17, 2001
Generic Available	No
Dosage forms	**Tablets**: 500/20 mg , 750/20 mg, 1000/20 mg
General Dosing Guidelines	The usual recommended starting dose for extended-release niacin tablets is 500 mg at bedtime. Niacin extended-release tablets must be titrated and the dose should not be increased by more than 500 mg every 4 weeks up to a maximum dose of 2000 mg/day, to reduce the incidence and severity of side effects. Patients already receiving a stable dose of niacin extended-release tablets may be switched directly to a niacin-equivalent dose of niacin extended-release/lovastatin tablets. The usual recommended starting dose of lovastatin is 20 mg once/day. Make dose adjustments at intervals of 4 weeks or more. Patients already receiving a stable dose of lovastatin may receive concomitant dosage titration with niacin extended-release tablets, and switch to niacin extended-release/lovastatin tablets once a stable dose of niacin extended-release tablets has been reached.
FDA Labeled Indications	Primary hypercholesterolemia/mixed dyslipidemia:
Pediatric Labeling	Not indicated
Other studies uses	None

HMG-COA Reductase Inhibitor Combinations	
Characteristic	**Advicor (lovastatin plus niacin extended release)**
Contraindications	• Prior hypersensitivity to niacin or to lovastatin or other HMG-CoA reductase inhibitors • Pregnancy • Breastfeeding period • Active peptic ulcer disease (exacerbation) • Active liver disease or unexplained persistent transaminase elevations (exacerbation) • Arterial bleeding (exacerbation; niacin component)
Major AE/Warnings	• Flushing • GI distress /History of peptic ulcer disease (risk of activation/recurrence) • Thrombocytopenia • Hyperglycemia • Headache
Dosage in Special Populations	The efficacy and safety of fixed-dose extended-release niacin/lovastatin have been similar regardless of age (Prod Info Advicor(R), 2001). No dose adjustment is required in elderly patients with relatively normal renal/hepatic function.
Unique Features	Combination product that combines two agents that work synergistically with one another to decrease lipid profile

SUMMARY of the HMG-CoA Reductase Inhibitors						
Approximate Dosage Equivalents						
Approximate equipotent dose (based on LDL-C reduction)	**Lescol**	**Mevacor**	**Pravastatin**	**Zocor**	**Lipitor**	**Crestor**
	20mg	10mg	10mg	5mg	X	N/a
	40mg	20mg	20mg	10mg	5mg (1/2 of 10 mg tab)	N/a
	80mg	40mg	40mg	20mg	10mg	N/a
	X	80mg	80mg	40mg	20mg	
	X	X		80mg	40mg	
	x	X			80mg	

Generalized Pharmacologic Summary						
	Lescol	**Mevacor**	**Pravastatin**	**Zocor**	**Lipitor**	**Crestor**
Natural/Synthetic	Synthetic	Natural	Natural	Semi-Synthetic	Synthetic	Synthetic
Hydrophilic/ Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Lipophilic	Hydrophilic
Metabolism	CYP2C9	CYP3A4	None via CYP No significant Drug interactions	CYP3A4	CYP3A4	CYP2C9
Structure	Structurally Similar				Structurally different	Structurally different

EFFICACY STUDIES

Drug Regimens	N	Demographics	Design and Duration	Primary End Points	Results/Comments
PRIMARY PREVENTION TRIALS					
Placebo Lovastatin 20-40mg/day (50% titrated to40mg/day for LDL >110mg/dL at 3 months) AFCAPS/TEXCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study	3301 3304	Men aged 45-73 yrs, and postmenopausal women aged 55-73, yrs w/o CAD, average TC & LDL levels, and low HDL: TC 180-264mg/dL, TG<400mg/dL, LDL 130-190mg/dL,(or 125-129 if TC/HDL-C > 6), HDL (men=45mg/dL, women=47mg/dL) Baseline demographics: angina 0%, DM 2%, HTN 22%, smoking 12%, aspirin 17%, B-blocker 5%, CCB 5%, estrogen 29.3% of women Mean age=58 yrs, 85% men, Mean LDL=150mg/dL	Prospective, MC, RCT, DB, PC. Intent-to-treat analysis. Mean duration = 5.2 yrs	Primary First acute major coronary event, (including fatal or nonfatal MI, unstable angina, or sudden cardiac death) Secondary Fatal/nonfatal CV events. PTCA/CABG. Fatal or nonfatal MI	Regimen 1st major coronary event Fatal/nonfatal CV events PTCA/ CABG Placebo 5.5% 7.7% 4.8% Lova 3.5%* 5.9%* 3.2%* *P<0.01 LDL decreased by 25% at 1 yr
Placebo Pravastatin 40mg/day WOSCOPS (West of Scotland Coronary Prevention Study)	3293 3302	Men aged 45 – 64 yrs w/ no history of MI and: LDL=155mg/dL. Baseline demographics: angina 5%, DM 1%, HTN 16%, smoking 44%, medications not listed. Mean age=55 yrs, 100% men, Mean LDL=192mg/dL.	Prospective, MC, RCT, DB, PC. Intent-to-treat analysis. Mean duration = 4.9 yrs	Primary First non-fatal MI/CAD death Secondary PTCA/CABG	Regimen 1st non-fatal MI/CAD death PTCA/CABG Placebo 7.9% 4.8% Prava 5.5%* 3.2%* *P<0.001 LDL-C decreased by 26%

Drug Regimens	N	Demographics	Design and Duration	Primary End Points	Results/Comments
Placebo -total population Placebo (primary prevention) Simvastatin 40mg/day - total population Simvastatin 40mg/day (primary prevention) HPS (Heart Protection Study) Presented are total population studied and subgroup - evaluating only the patients without Prior MI or Other CHD at time of study entry.	10267 (3575) 10269 (3575)	Men and women 40-80 yrs w/ TC ≥ 135mg/dL and were considered to be at substantial 5-yr risk of death from CHD because of a past medical history of: (i) CAD; or (ii) occlusive disease of non-coronary arteries; (iii) DM; or (iv) treated HTN if also male and aged at least 65 yrs. Age > 70 yrs = 28.2%, 75% men, Mean LDL=148mg/dl.	Run-in treatment involved 4 wks of placebo followed by 4-6 wks simvastatin 40mg Prospective, MC, RCT, DB, PC. Intent-to-treat analysis. Mean duration = 5 yrs	Primary (total population) All cause mortality. CV mortality. Non-CV mortality. Secondary Major coronary events (non-fatal MI or death from CAD) in subpopulation without CAD at baseline	Regimen All cause mortality CV mortality Major CV events (in subset without CAD at baseline) Placebo 14.7% 9.1% 20.8% Simva 12.9%* 7.6%* 16.1%* P<0.001 No increase risk of neoplastic deaths (simva 3.5%, placebo 3.4%). LDL decreased by 26% over 5 yrs.
Placebo –total population Placebo (primary prevention) Pravastatin 40mg/day–total population Pravastatin (primary prevention) PROSPER study Presented are total population studied and subgroup - evaluating only the patients without Prior MI or Other CVD at time of study entry.	2913 (1654) 2891 (1585)	Men and women 70-82 yrs w/CVD or raised risk such as DM, HTN, smoking TC 159-351mg/dL. Ave age 75yrs, 48% men, Mean LDL=148mg/dl.	Run-in treatment involved 4 wks of placebo. Prospective, MC, RCT, DB, PC. Intent-to-treat analysis. Mean duration = 3.2 yrs	Primary CHD death, or non-fatal MI, or fatal or non-fatal stroke. Safety assessment of new cancers.	Regimen Primary endpoint in the primary prevention subgroup Placebo 12.1% Prava 11.4% Non-significant difference in primary endpoint. LDL decrease 27% ave. over first 5 yrs New diagnosis of cancer occurred 6.9% of placebo pts and 8.6% of pravastatin pts (p=0.02), for a significantly higher rate of new cancer diagnoses in the pravastatin group.

Drug Regimens	N	Demographics	Design and Duration	Primary End Points	Results/Comments
Placebo Pravastatin 40mg/day (In 6 % of patients, LDL = 175mg/dL, added cholestyramine 8-16 g) CARE (Cholesterol and Recurrent Events Trial)	2078 2081	Men and postmenopausal women aged 21 –75 yrs with a history of an acute MI 3-20 months before randomization and: TC < 240mg/dL, TG <350mg/dL, LDL-C 115-174mg/dL Baseline demographics: angina 21% DM 15% HTN 43% smoking 21% aspirin 83% B-blocker 39% CCB 38% nitrates 33% estrogen 9.4% of women Mean age=59 yrs, 86% men, Mean LDL=139mg/dl.	Prospective, MC, RCT, DB, PC. Intent-to-treat analysis. Median duration = 5 yrs	Primary CAD death or non-fatal MI Secondary PTCA/CABG Fatal/non-fatal MI Stroke	Regimen CAD death or non-fatal MI PTCA / CABG Fatal or non-fatal MI Stroke Placebo 13.2% 18.8% 10% 3.8% Prava 10.2%* 14.1%* 7.5%* 2.6%* *P<0.01 LDL decreased by 28% over 5 yrs
Placebo –total population Placebo (secondary prevention) Pravastatin 40mg/day–total population Pravastatin (secondary prevention) PROSPER (Prospective study of Pravastatin in the Elderly at Risk)	2913 (1259) 2891 (1306)	Men and women 70-82 yrs w/CVD or raised risk such as DM, HTN, smoking TC 159-351mg/dL. Ave age 75yrs, 48% men, Mean LDL=148mg/dl. Presented are total population studied and subgroup - evaluating only the patients with Prior MI or Other CVD at time of study entry.	Run-in treatment involved 4 wks of placebo. Prospective, MC, RCT, DB, PC. Intent-to-treat analysis. Mean duration = 3.2 yrs	<u>Primary</u> CHD death, or non-fatal MI, or fatal or non-fatal stroke. Safety assessment of new cancers.	Regimen Primary endpoint in the primary prevention subgroup Placebo 21.7% Prava 17.4%* *P<0.05. New diagnosis of cancer occurred in 6.9% of placebo pts and 8.6% of pravastatin pts (p=0.02), for a significantly higher rate of new cancer diagnoses in the pravastatin group. LDL decrease 27% ave. over first 5 yrs.

Drug Regimens	N	Demographics	Design and Duration	Primary End Points	Results/Comments
Placebo -total population Placebo (secondary prevention) Simvastatin 40mg/day - total population Simvastatin 40mg/day (secondary prevention) HPS (Heart Protection Study) Presented are total population studied and subgroup - evaluating only the patients with Prior MI or Other CHD at time of study entry.	10267 (6692) 10269 (6694)	Men and women 40-80 yrs w/ TC ≥ 135mg/dL and were considered to be at substantial 5-yr risk of death from CHD because of a past medical history of: (i) CAD; or (ii) occlusive disease of non-coronary arteries; (iii) DM; or (iv) treated HTN if also male and aged at least 65 yrs. Age > 70 yrs = 28.2%, 75% men, Mean LDL=148mg/dl.	Run-in treatment involved 4 wks of placebo followed by 4-6 wks simvastatin 40mg Prospective, MC, RCT, DB, PC. Intent-to-treat analysis. Mean duration = 5 yrs	<u>Primary (total population)</u> All cause mortality. CV mortality. Non-CV mortality. <u>Secondary</u> Major coronary events (non-fatal MI or death from CAD) in subpopulation with CAD at baseline	Regimen All cause mortality CV mortality Major CV events (in subset with CAD at baseline) Placebo 14.7% 9.1% 27.5% Simva 12.9%* 7.6%* 21.8%* P<0.001 No increase risk of neoplastic deaths (simva 3.5%, placebo 3.4%). LDL decreased by 26% over 5 yrs.

Drug Regimens	N	Demographics	Design and Duration	Primary End Points	Results/Comments
Placebo Simvastatin 20-40mg qd (37% titrated to 40mg at 6 months to LDL goal) 4S (Scandinavian Simvastatin Survival Study)	2223 2221	Men and women aged 35-70 yrs w/ a history of angina pectoris or acute MI > 6 months ago and: TC 213-309mg/dL, TG = 221mg/dL. Baseline demographics: angina 21% DM 5%, HTN 26%, smoking 26%, aspirin 37%, B-blocker 57%, CCB 31%, nitrates 32%. Mean age=58 yrs, 81% men, Mean LDL=188mg/dL	Prospective, MC, RCT, DB, PC. Intent-to-treat analysis. Mean duration = 5.4 yrs	Primary: Total mortality Secondary: Major coronary events PTCA/CABG	Regimen Mortality Major Coronary Events PTCA/ CABG Placebo 12% 28% 17.2% Simva 8%* 19%* 11.3%* P<0.001 LDL-C decreased by 35% at 5.4 years

Drug Regimens	N	Demographics	Design and Duration	Primary End Points	Results/Comments
Placebo Atorvastatin 10mg qd (no dose titration) ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial)	5137 5168	Men and women aged 40-79 yrs w/ either untreated HTN (BP>160/100 mmHg) or treated HTN (BP<140/90 mmHg) and TC < 250mg/dl not currently taking statin or fibrate. In addition, patients needed to have 3 or more of the following: LVH, ECG changes (excluding evidence of previous MI), type 2 DM, PAD, h/o stroke or TIA, male, age ≥ 55 yrs, microalbuminuria or proteinuria, smoking, HDL to TC ratio ≥ 6, or premature family history of CHD. Excluded if: h/o previous MI, currently treated angina, CVA in past 3 months, trigs > 250 mg/dl, heart failure, uncontrolled arrhythmia, or any clinically important hematological or biochemical abnormality on routine screening. Mean age=63 yrs, 81% men, Mean LDL=132mg/dL	Prospective, MC, RCT, DB, PC. Intent-to-treat analysis. Mean duration = 3.3 yrs (stopped prematurely due to benefit with atorvastatin)	Primary: Combined endpoint of non-fatal MI, including so-called silent MI, and fatal CHD Secondary: Primary outcome without silent MI, all cause mortality, total CV events, fatal and non-fatal stroke, fatal and non-fatal heart failure	Regimen Combined endpoint‡ All cause death Total CV events Stroke HF Placebo 3.0% 4.1% 4.8% 2.4% 0.7% Atorva 1.9%* 3.6% 3.4* 1.7%† 0.8% *P<0.001 †P<0.05 ‡ removing silent-MI did not change results LDL-C decreased by 33% at 3.3 years

Drug Regimens	N	Demographics	Design and Duration	Primary End Points	Results/Comments
Placebo Fluvastatin 40mg BID FLARE (Fluvastatin Angiographic Restenosis Trial)	834 total pts	Men and women w/ symptomatic or ischemia-producing coronary lesions suitable for balloon angioplasty and: LDL < 232mg/dL, TG = 399mg/dL and aspirin 325mg/day for all patients. Baseline demographics: angina 88%, DM 5%, HTN 33%, smoking 29%, single vessel disease 85%, stable class 0-2 angina 71%. Mean age=61 yrs, 83% men, Mean LDL=153mg/dL,	Duration = 26 weeks	Primary Restenosis (absolute change in medial lumen diameter [MLD]) Secondary Death and non-fatal-MI	Primary Endpoint Restenosis -not significant Significant Secondary Endpoints Death and non-fatal MI (1.4% in patients on fluvastatin vs. 4% with placebo; p=0.03) LDL decreased 33%
Placebo Lovastatin 20mg/day (lovastatin titrated to 40mg/day, then 40mg BID if LDL > 130mg/dl) CCAIT (Canadian Coronary Atherosclerosis Intervention Trial)	166 165	Men and women up to 70 yrs, high risk for CAD or w/ CAD and TC 220-330mg/dl. Mean LDL=173mg/dl,	Prospective, MC, RCT, DB, PC. Not intent-to-treat analysis. Duration = 2 yrs.	Primary Comparison between groups of coronary change score per-pt mean of the MLD for all lesions measured as determined by coronary angiography.	Primary Endpoint Progression of lesions (defined as ≥ 4 mm of one or more lesions) occurred in 62 of 146 lovastatin patients and 86 of 153 placebo patients, p=0.018. CCAIT was not designed to detect differences in clinical events. Non-significant trend toward lower events in lovastatin group. LDL decreased 29%.

Drug Regimens	N	Demographics	Design and Duration	Primary End Points	Results/Comments
Placebo Pravastatin 20–40mg/day Pooled analysis of angiographic trials (PLAC I, PLAC II, REGRESS, KAPS)	936 955	Patients (men and women in PLAC I & II, men in REGRESS and KAPS) with coronary atherosclerosis and: PLAC I & II: LDL 130-189mg/dL, TG < 400mg/dL REGRESS: TC 155-309mg/dL, TG = 355mg/dL KAPS: LDL > 155mg/dL, TG < 400mg/dL Baseline demographics: HTN 33%, post-MI 38%, smoking 24% Mean age=57 yrs, 94% men, Mean LDL=171mg/dL,	Pooled Analysis of 4 studies. Prospective, MC, RCT, DB, PC. Intent-to-treat analysis. Mean duration =2-3 yrs	Primary None, this was a pooled analysis report.	Significant Combined Endpoints (Pooled Analysis) Fatal/non-fatal MI (pravastatin 2.4% vs. placebo 6.4%; p=0.001) Nonfatal MI or CHD death (pravastatin 3.4% vs. placebo 7.1%; p=0.006) All cause mortality (pravastatin 1.8% vs. placebo 3.3%; p=0.003) Non-fatal MI , all cause mortality, stroke, PTCA/CABG (pravastatin 13.7% vs. placebo 19.5%; p=0.002) LDL decreased 28%
Placebo Simvastatin 20mg/day titrated to 40mg/day if LDL>90mg/dl. CIS (Coronary Intervention Study)	254 total pts	Men and women 21 yrs and >, atherosclerosis in 3 or > coronary segments and TC=160-240mg/dl. Mean LDL=165mg/dl	Prospective, MC, RCT, DB, PC. Intent-to-treat analysis. Duration=2.3 yrs.	Primary Global change score and the % mean change in MLD assessed by angiography. Clinical events spontaneously reported.	There were no statistical differences in clinical events between groups. LDL decreased 31%.

MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial.

Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group.

Lancet. 2003 Jun 14;361(9374):2005-16.

Abstract

BACKGROUND: Individuals with diabetes are at increased risk of cardiovascular morbidity and mortality, although typically their plasma concentrations of LDL cholesterol are similar to those in the general population. Previous evidence about the effects of lowering cholesterol in people with diabetes has been limited, and most diabetic patients do not currently receive cholesterol-lowering therapy despite their increased risk. METHODS: 5963 UK adults (aged 40-80 years) known to have diabetes, and an additional 14573 with occlusive arterial disease (but no diagnosed diabetes), were randomly allocated to receive 40 mg simvastatin daily or matching placebo. Prespecified analyses in these prior disease subcategories, and other relevant subcategories, were of first major coronary event (ie, non-fatal myocardial infarction or coronary death) and of first major vascular event (ie, major coronary event, stroke or revascularisation). Analyses were also conducted of subsequent vascular events during the scheduled treatment period. Comparisons are of all simvastatin-allocated versus all placebo-allocated participants (ie, intention to treat), which yielded an average difference in LDL cholesterol of 1.0 mmol/L (39 mg/dL) during the 5-year treatment period. FINDINGS: Both among the participants who presented with diabetes and among those who did not, there were highly significant reductions of about a quarter in the first event rate for major coronary events, for strokes, and for revascularisations. For the first occurrence of any of these major vascular events among participants with diabetes, there was a definite 22% (95% CI 13-30) reduction in the event rate (601 [20.2%] simvastatin-allocated vs 748 [25.1%] placebo-allocated, $p<0.0001$), which was similar to that among the other high-risk individuals studied. There were also highly significant reductions of 33% (95% CI 17-46, $p=0.0003$) among the 2912 diabetic participants who did not have any diagnosed occlusive arterial disease at entry, and of 27% (95% CI 13-40, $p=0.0007$) among the 2426 diabetic participants whose pretreatment LDL cholesterol concentration was below 3.0 mmol/L (116 mg/dL). The proportional reduction in risk was also about a quarter among various other subcategories of diabetic patient studied, including: those with different duration, type, or control of diabetes; those aged over 65 years at entry or with hypertension; and those with total cholesterol below 5.0 mmol/L (193 mg/dL). In addition, among participants who had a first major vascular event following randomisation, allocation to simvastatin reduced the rate of subsequent events during the scheduled treatment period. INTERPRETATION: The present study provides direct evidence that cholesterol-lowering therapy is beneficial for people with diabetes even if they do not already have manifest coronary disease or high cholesterol concentrations. Allocation to 40 mg simvastatin daily reduced the rate of first major vascular events by about a quarter in a wide range of diabetic patients studied. After making allowance for non-compliance, actual use of this statin regimen would probably reduce these rates by about a third. For example, among the type of diabetic patient studied without occlusive arterial disease, 5 years of treatment would be expected to prevent about 45 people per 1000 from having at least one major vascular event (and, among these 45 people, to prevent about 70 first or subsequent events during this treatment period). Statin therapy should now be considered routinely for all diabetic

patients at sufficiently high risk of major vascular events, irrespective of their initial cholesterol concentrations.

Rosuvastatin--a highly effective new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor: review of clinical trial data at 10-40 mg doses in dyslipidemic patients.

Schuster H.

Cardiology. 2003;99(3):126-39.

MDC, Humboldt University, Berlin, Germany.

Abstract
Rosuvastatin (Crestor; licensed to AstraZeneca, Macclesfield, UK from Shionogi, Osaka, Japan) is a new statin with pharmacologic characteristics that translate into selectivity of effect in hepatic cells and enhanced potency in 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition. It is approved for use at doses of 10-40 mg once daily to reduce low-density lipoprotein (LDL) cholesterol, increase high-density lipoprotein (HDL) cholesterol and improve other lipid measures in dyslipidemic patients. In a dose-ranging study in mild/moderate hypercholesterolemia, rosuvastatin reduced LDL cholesterol by 52-63% at 10-40 mg. Rosuvastatin 10 mg reduces LDL cholesterol significantly more than atorvastatin 10 mg, simvastatin 10-40 mg and pravastatin 10-40 mg, and enables significantly more patients to achieve National Cholesterol Education Program and Joint European Societies LDL cholesterol goals compared with each of these statins. Rosuvastatin also produces marked elevations in HDL cholesterol and maintains this effect across the dose range. Rosuvastatin favorably modifies triglycerides, LDL cholesterol and other lipid measures in patients with hypertriglyceridemia or mixed dyslipidemia, including diabetic patients, and may constitute a monotherapy option for many such patients. Rosuvastatin is well tolerated when used alone or in combination, exhibiting a safety profile similar to that of other available statins. Rosuvastatin offers considerable advantages for use in routine clinical practice. Copyright 2003 S. Karger AG, Basel

Preclinical and clinical pharmacology of Rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor.

McTaggart F, Buckett L, Davidson R, Holdgate G, McCormick A, Schneck D, Smith G, Warwick M.

Am J Cardiol. 2001 Mar 8;87(5A):28B-32B.

AstraZeneca, Alderley Park, Cheshire, United Kingdom.
Abstract

Rosuvastatin (formerly ZD4522) is a new 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) with distinct pharmacologic properties. Compared with most other statins, it is relatively hydrophilic, similar in this respect to pravastatin. Rosuvastatin has been

shown to be a comparatively potent inhibitor of HMG-CoA reductase activity in a purified preparation of the catalytic domain of the human enzyme, as well as in rat and human hepatic microsomes. In rat hepatocytes, rosuvastatin was found to have significantly higher potency as an inhibitor of cholesterol synthesis than 5 other statins. Rosuvastatin was approximately 1,000-fold more potent in rat hepatocytes than in rat fibroblasts. Further studies in rat hepatocytes demonstrated that rosuvastatin is taken up into these cells by a high-affinity active uptake process. Rosuvastatin was also taken up selectively into the liver after intravenous administration in rats. Potent and prolonged HMG-CoA reductase inhibitory activity has been demonstrated after oral administration to rats and dogs. Pharmacokinetic studies in humans using oral doses of 5 to 80 mg showed that maximum plasma concentrations and areas under the concentration-time curve are approximately linear with dose. The terminal half-life is approximately 20 hours. Studies with human hepatic microsomes and human hepatocytes have suggested little or no metabolism via the cytochrome P-450 3A4 isoenzyme. On the basis of these observations, it is suggested that rosuvastatin has the potential to exert a profound effect on atherogenic lipoproteins.